FORM PTO-1390 (REV. 10-2000)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER 20430P
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 09/937499

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/09587	10 April 2000	14 April 1999

TITLE OF INVENTION

NOVEL HUMAN VOLTAGE-GATED POTASSIUM CHANNEL

APPLICANT(S) FOR DO/EO/US

Konstantin Petrukhin, C. Thomas Caskey, Wen Li and Michael L. Metzker

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures [35 U.S.C. 371(f)] at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(l).
4. ☒ A proper Demand for International Preliminary Examination was made and the US was elected by the expiration of the 19th month from the earliest claimed priority date (PCT Article 31).
5. ☒ A copy of the International Application as filed [35 U.S.C. 371(c)(2)].
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed [35 U.S.C. 371(c)(2)].
7. ☐ Amendments to the claims of the International Application under PCT Article 19 [35 U.S.C. 371(c)(3)].
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)].
9. ☒ An oath or declaration of the inventor(s) [35 U.S.C. 371(c)(4)].
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 [35 U.S.C. 371(c)(5)].

Items 11 to 16 below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A **FIRST** preliminary amendment.
    ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

EXPRESS MAIL CERTIFICATE
DATE OF DEPOSIT Sept. 26, 2001
EXPRESS MAIL NO. EF180600684US
I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL "POST OFFICE TO ADDRESSEE" BEFORE 5 P.M. ON THE ABOVE DATE IN AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231
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DATE 9/26/01

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U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/937499	PCT/US00/20430	20430P

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE [37 CFR 1.492(a)(1)-(5)]:		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee [37 CFR 1.445(a)(2)] paid to USPTO and International Search Report not prepared by the EPO or JPO **$1,000.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee [37 CFR 1.445(a)(2)] paid to USPTO **$710.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$100.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date [37 CFR 1.492(e)].	$0.00	

Claims	Number Filed	Number Extra	Rate		
Total Claims	21 - 20 =	1	X **$18.00**	$18.00	
Independent Claims	12 - 3 =	9	X **$80.00**	$720.00	
Multiple dependent claim(s) (if applicable)		0	+ **$270.00**	$0.00	
TOTAL OF ABOVE CALCULATIONS =				$838.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.					
SUBTOTAL =				$838.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date [37 CFR 1.492(f)]. +				$0.00	
TOTAL NATIONAL FEE =				$838.00	
Fee for recording the enclosed assignment [37 CFR 1.21(h)]. The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property. +					
TOTAL FEES ENCLOSED =				$838.00	
				Amount to be refunded	
				charged	

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 13-2755 in the amount of $838.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to the Deposit Account No. 13-2755. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive [37 CFR 1.137(a) or (b)] must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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DATE: 9/26/01

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38,413
REGISTRATION NUMBER

TITLE OF THE INVENTION
NOVEL HUMAN VOLTAGE-GATED POTASSIUM CHANNEL

CROSS-REFERENCE TO RELATED APPLICATIONS

Not applicable.

STATEMENT REGARDING FEDERALLY-SPONSORED R&D

Not applicable.

REFERENCE TO MICROFICHE APPENDIX

Not applicable.

FIELD OF THE INVENTION

The present invention is directed to novel human DNA sequences encoding a voltage-gated potassium channel.

BACKGROUND OF THE INVENTION

Voltage-gated potassium channels form transmembrane pores that open in response to changes in cell membrane potential and selectively allow potassium ions to pass through the membrane. Many voltage-gated potassium channels have been identified. They are distinguishable by tissue-specific patterns of expression as well as by electrophysiological and pharmacological properties.

Voltage-gated potassium channels have been shown to be involved in maintaining cell membrane potentials and controlling the repolarization of action potentials in many cells, *e.g.*, neurons, muscle cells, and pancreatic β cells. They are important targets for drug discovery in connection with a variety of diseases.

Functional voltage-gated potassium channels are believed to be tetramers of four alpha subunits, each of which contains six transmembrane spanning segments. The alpha subunits making up a tetramer may be the same (in the case of homotetramers) or may be different (in the case of heterotetramers). The membrane-spanning alpha subunits making up the tetramers may sometimes be associated with additional, beta subunits, which may alter the behavior of the tetramers.

For reviews of voltage-gated potassium channels see Robertson, 1997, Trends Pharmacol. Sci. 18:474-483; Jan & Jan, 1997, J. Physiol. 505:267-282; Catterall, 1995, Ann. Rev. Biochem. 64:493-531.

Macular dystrophy is a term applied to a heterogeneous group of diseases that collectively are the cause of severe visual loss in a large number of people. A common characteristic of macular dystrophy is a progressive loss of central vision resulting from the degeneration of the pigmented epithelium underlying the retinal macula. In many forms of macular dystrophy, the end stage of the disease results in legal blindness. More than 20 types of macular dystrophy are known: e.g., age-related macular dystrophy, Stargardt's and Stargardt-like macular dystrophy, cone-rod dystrophies, atypical vitelliform macular dystrophy (VMD1), Usher Syndrome Type 1B, autosomal dominant neovascular inflammatory vitreoretinopathy, familial exudative vitreoretinopathy, and Best's macular dystrophy. For a review of the macular dystrophies, see Sullivan & Daiger, 1996, Mol. Med. Today 2:380-386.

Cone-rod dystrophies involve an initial loss of cone photoreceptors followed by the degeneration of rod photoreceptors. This loss of photoreceptors can lead to blindness. Cone-rod dystrophies appear to be a heterogeneous group of inherited disorders for which multiple chromosomal locations have been implicated (Evans et al., 1994, Nature Genet. 6:210-213; Kelsell et al., 1997, Hum. Mol. Genet. 6:597-600). In particular, Kelsell et al., 1998, Am. J. Hum. Genet. 63:274-279 found a candidate gene (CORD7) located at chromosome 6q in a four-generation British family affected with cone-rod dystrophy. A marker in 6q, D6S280, showed a high LOD score of 3.31 (at genetic distance = 0).

Stargardt-like macular dystrophy is an inherited, dominant retinal disease. Affected individuals have normal vision in early childhood but show impaired central vision either in late childhood or early adulthood. The first observable characteristics of the disease are flecks seen in the macula. This is followed by central atrophy, resulting in visual acuity decreasing to 20/200 or worse (Stone et al., Arch. Ophthalmol. 112:765-772 [Stone]). Stone mapped a gene responsible for Stargardt-like macular dystrophy to chromosome 6q. The marker D6S280 was observed by Stone to have the high LOD score of 5.5 (at genetic distance = 0).

Cone-rod dystrophy and Stargardt-like macular dystrophy appear different from a clinical perspective. For example, Stargardt-like macular dystrophy

generally begins in childhood and involves white/yellow flecks in the retina while cone-rod dystrophy is an adult-onset disorder in which no flecks are present. Despite such clinical differences, both diseases may be caused by mutations in the same gene. It is not uncommon for different mutations in a single gene to give rise to clinically different disorders. For example, depending upon the particular mutation, mutations in the peripherin/RDS gene can give rise to either butterfly-shaped pigment dystrophy of the fovea, retinitis pigmentosa, pattern dystrophy, flavus maculatus, macular dystrophy, or central areolar choroidal dystrophy (Nichols et al., 1993, Nature Genet. 3:202-207; Weleber et al., 1993, Arch. Ophtalmol. 111:1531-1542; Wells et al., 1993, Nature Genet. 3:213-218; Reig et al., 1995, Ophthalmic. Genet. 16:39-44).

While studies of macular dystrophies such as cone-rod dystrophy or Stargardt-like macular dystrophy are valuable in themselves, such studies are also valuable in that they are expected to shed light on age-related macular degeneration (AMD). AMD is the leading cause of severe visual loss in older individuals. Genetic factors apparently play a role in AMD (Hyman et al., 1983, Am. J. Epidemiol. 118:213-227; Gass, 1973, Arch. Ophthamol. 90:206-217). It is believed likely that mild allelic variations of such earlier-onset diseases as cone-rod dystrophy and Stargardt-like macular dystrophy are responsible for some cases of AMD. Thus, understanding and developing treatments for these earlier-onset diseases should prove valuable with respect to AMD as well.

Salla disease is a recessive condition characterized by early-onset psychomotor retardation and ataxia that involves defects in the lysosomal transport of sialic acid. Leppänen et al., 1996, Genomics 37:62-67 (Leppänen) located the gene for Salla disease in the immediate vicinity of the marker D6S280. Leppänen screened a PAC library with the marker D6S280 and obtained three positive clones, among which were PAC 141B1 and PAC 224H23, strongly suggesting that the gene for Salla disease is present on these PACs.

SUMMARY OF THE INVENTION

The present invention is directed to novel human DNA sequences encoding a voltage-gated potassium channel, KCNQ5, located in a chromosomal region that contains a gene associated with Stargardt-like macular dystrophy, cone-rod macular dystrophy, and Salla disease.

The present invention includes genomic KCNQ5 DNA as well as cDNA that encodes the KCNQ5 protein. The human genomic KCNQ5 DNA is substantially free from other nucleic acids and has the nucleotide sequence shown in SEQ.ID.NO.:1. The human cDNA encoding KCNQ5 protein is substantially free from other nucleic acids and has the nucleotide sequence shown in SEQ.ID.NO.:2. Also provided is KCNQ5 protein encoded by the novel DNA sequences. The human KCNQ5 protein is substantially free from other proteins and has the amino acid sequence shown in SEQ.ID.NO.:3. Methods of expressing KCNQ5 protein in recombinant systems are provided as well as methods of identifying activators and inhibitors of KCNQ5 protein function. Also provided are diagnostic methods that detect carriers of mutant KCNQ5 genes.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A-AO shows the genomic DNA sequence of human KCNQ5 (SEQ.ID.NO.:1). Underlined nucleotides in capitals represent exons. The start ATG codon in exon 1 and the stop TAA codon in exon 14 are shown in bold italics. The D6D280 genetic marker and a phosphoglycerate pseudogene are underlined in bold. The exact lengths of the gaps between exons 1 and 2, 2 and 3, 10 and 11, 11 and 12, 12 and 13, and 13 and 14 are unknown. These gaps are represented as runs of ten bold ns for the sake of convenience.

Figure 2A-E shows the nucleotide sequence (SEQ.ID.NO.:2) and encoded amino acid sequence (SEQ.ID.NO.:3) of human KCNQ5 cDNA. The ATG start codon is at position 138; the TAA stop codon is at position 2,676.

Figure 3A shows the results of a Northern blot of KCNQ5 mRNA expression in various human tissues. Figure 3B shows the results of RT-PCR analysis of KCNQ5 mRNA expression in various human tissues.

Figure 4A shows a sequence alignment of human KCNQ5 protein (SEQ.ID.NO.:3) with human KCNQ4 protein (SEQ.ID.NO.:4). The consensus sequence shown is (SEQ.ID.NO.:5). Figure 4B-C shows a multiple sequence alignment between human KCNQ5 protein (SEQ.ID.NO.:3), human KCNQ1 protein (SEQ.ID.NO.:43), human KCNQ2 protein (SEQ.ID.NO.:6), human KCNQ3 protein (SEQ.ID.NO.:7), and human KCNQ4 protein (SEQ.ID.NO.:4). The consensus sequence shown is (SEQ.ID.NO.:8).

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of this invention:

"Substantially free from other proteins" means at least 90%, preferably 95%, more preferably 99%, and even more preferably 99.9%, free of other proteins. Thus, a KCNQ5 protein preparation that is substantially free from other proteins will contain, as a percent of its total protein, no more than 10%, preferably no more than 5%, more preferably no more than 1%, and even more preferably no more than 0.1%, of non- KCNQ5 proteins. Whether a given KCNQ5 protein preparation is substantially free from other proteins can be determined by such conventional techniques of assessing protein purity as, *e.g.*, sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) combined with appropriate detection methods, *e.g.*, silver staining or immunoblotting.

"Substantially free from other nucleic acids" means at least 90%, preferably 95%, more preferably 99%, and even more preferably 99.9%, free of other nucleic acids. Thus, a KCNQ5 DNA preparation that is substantially free from other nucleic acids will contain, as a percent of its total nucleic acid, no more than 10%, preferably no more than 5%, more preferably no more than 1%, and even more preferably no more than 0.1%, of non- KCNQ5 nucleic acids. Whether a given KCNQ5 DNA preparation is substantially free from other nucleic acids can be determined by such conventional techniques of assessing nucleic acid purity as, *e.g.*, agarose gel electrophoresis combined with appropriate staining methods, *e.g.*, ethidium bromide staining, or by sequencing.

A "conservative amino acid substitution" refers to the replacement of one amino acid residue by another, chemically similar, amino acid residue. Examples of such conservative substitutions are: substitution of one hydrophobic residue (isoleucine, leucine, valine, or methionine) for another; substitution of one polar residue for another polar residue of the same charge (*e.g.*, arginine for lysine; glutamic acid for aspartic acid); substitution of one aromatic amino acid (tryptophan, tyrosine, or phenylalanine) for another.

A polypeptide has "substantially the same biological activity as KCNQ5" if that polypeptide conducts a voltage-gated potassium current when expressed in appropriate cell types and has an amino acid sequence that is at least about 50% identical to SEQ.ID.NO.:3 when measured by such standard programs as BLAST or FASTA.

The present invention relates to the identification and cloning of KCNQ5, a gene encoding a novel voltage-gated potassium channel. The human KCNQ5 gene is located on chromosome 6q14, in a chromosomal region that contains genes that have been linked with the occurrence of at least three diseases: Stargardt-like macular dystrophy, cone-rod dystrophy, and Salla disease.

The human KCNQ5 gene is present on PAC clones from chromosomal region 6q14. PAC141B1 was sequenced and KCNQ5 was found based on homology between the genomic sequences of KCNQ5 present in PAC 141B1 and the sequences of known potassium channel genes. PAC 141B1 is available from Research Genetics, Inc., Huntsville, AL, as an individual clone from the RPCI4,5,6 Library (catalog number CTLI.C). Using PCR primers derived from the KCNQ5 sequence, a cDNA sequence representing the coding region as well as a large portion of the 3'-UTR of KCNQ5 was isolated from a human fetal brain cDNA library. Comparison of this cDNA clone with the genomic sequences present in PAC141B1, as well as KCNQ5 sequences found in PAC224H23, showed that exons 3-11 and portions of flanking intronic regions are present in PAC141B1. Exon 2 and flanking intronic regions were found in PAC224H23, while the rest of the KCNQ5 gene (exons 1, 12-14, and flanking intronic regions) was recovered from total human genomic DNA by using cDNA primers and a GenomeWalker kit from Clontech, Palo Alto, CA.

PAC141B1 and PAC224H23 are located in the region of the Salla disease gene (Leppänen et al., 1996, Genomics 37:62-67). PAC141B1 contains the polymorphic genetic marker D6S280 that is located in intron 3 of the KCNQ5 gene between exons 3 and 4 (Figure 1). D6S280 is the marker that detects the maximum LOD score of 5.5 (at genetic distance = 0) in families with Stargardt-like macular dystrophy (Stone et al., Arch. Ophthalmol. 112:765-772). D6S280 also detects a LOD score of 3.31 (at genetic distance = 0) in families with cone-rod dystrophy (Kelsell et al., 1998, Am. J. Hum. Genet. 63:274-279). These LOD scores indicate that D6S280 is very closely linked to, and probably is within, the gene for Stargardt-like macular dystrophy and cone-rod dystrophy. In view of these findings, it is likely that KCNQ5 is involved in Salla disease, Stargardt-like macular dystrophy, and cone-rod dystrophy.

That KCNQ5 should be involved with these three diseases is consistent with its expression pattern (see Figure 3A-B) which shows that KCNQ5 is expressed predominately in the retina and brain, in addition to being expressed in the

skeletal muscle. Stargardt-like macular dystrophy and cone-rod dystrophy are inherited retinal diseases while Salla disease is a disorder that is characterized by early onset psychomotor retardation and ataxia.

Bioinformatic analysis revealed a striking homology of the KCNQ5 protein to a group of voltage gated potassium channels (KCNQ1, KCNQ2, KCNQ3, and KCNQ4; see Figure 4A-B). All of the typical amino acid motifs of these potassium channels are preserved in KCNQ5. A Kyte-Doolittle algorithm analysis predicts a transmembrane organization for KCNQ5 that is typical for this group of potassium channels. Mutations in members of this family of potassium channels have been shown to result in inherited disease (KCNQ2 and KCNQ3, epilepsy [Biervert et al., 1998, Science 279:403-406; Singh et al., 1998, Nature Genet. 18:25-29; Schroeder et al., Nature 1998, 396:687-690]; KCNQ4, a form of nonsyndromic dominant deafness [Kubisch et al., 1999, Cell 96:437-446], KCNQ1, congenital long QT syndrome which causes cardiac arrhythmias and sudden death [Splawski et al., 1997, N. Engl. J. Med. 336:1562-1567]).

The present invention provides DNA encoding KCNQ5 that is substantially free from other nucleic acids. The present invention also provides recombinant DNA molecules encoding KCNQ5. The present invention provides DNA molecules substantially free from other nucleic acids comprising the nucleotide sequence shown in Figure 1 as SEQ.ID.NO.:1. Analysis of SEQ.ID.NO.:1 revealed that this genomic sequence defines a gene having 14 exons. These exons collectively have an open reading frame that encodes a protein of 846 amino acids.

The present invention includes cDNA encoding KCNQ5 protein. Such a cDNA is shown in Figure 2 as SEQ.ID.NO.:2. The present invention therefore includes DNA comprising the nucleotide sequence SEQ.ID.NO.:2. The DNA can be isolated or substantially free of other DNA sequences.

The present invention includes DNA molecules substantially free from other nucleic acids comprising the coding region of SEQ.ID.NO.:2. Accordingly, the present invention includes DNA molecules substantially free from other nucleic acids having a sequence comprising positions 138-2,675 of SEQ.ID.NO.:2. Also included are recombinant DNA molecules having a nucleotide sequence comprising positions 138-2,675 of SEQ.ID.NO.:2 and isolated DNA molecules having a nucleotide sequence comprising positions 138-2,675 of SEQ.ID.NO.:2.

The novel DNA sequences of the present invention encoding KCNQ5, in whole or in part, can be linked with other DNA sequences, *i.e.*, DNA sequences to which KCNQ5 is not naturally linked, to form "recombinant DNA molecules" encoding KCNQ5. Such other sequences can include DNA sequences that control transcription or translation such as, *e.g.*, translation initiation sequences, promoters for RNA polymerase II, transcription or translation termination sequences, enhancer sequences, sequences that control replication in microorganisms, sequences that confer antibiotic resistance, or sequences that encode a polypeptide "tag" such as, *e.g.*, a polyhistidine tract or the myc epitope. The novel DNA sequences of the present invention can be inserted into vectors such as plasmids, cosmids, viral vectors, P1 artificial chromosomes, or yeast artificial chromosomes.

Included in the present invention are DNA sequences that hybridize to at least one of SEQ.ID.NO:1 or SEQ.ID.NO:2 under stringent conditions. By way of example, and not limitation, a procedure using conditions of high stringency is as follows: Prehybridization of filters containing DNA is carried out for 2 hr. to overnight at 65°C in buffer composed of 6X SSC, 5X Denhardt's solution, and 100 μg/ml denatured salmon sperm DNA. Filters are hybridized for 12 to 48 hrs at 65°C in prehybridization mixture containing 100 μg/ml denatured salmon sperm DNA and 5-20 X 10^6 cpm of ^{32}P-labeled probe. Washing of filters is done at 37°C for 1 hr in a solution containing 2X SSC, 0.1% SDS. This is followed by a wash in 0.1X SSC, 0.1% SDS at 50°C for 45 min. before autoradiography.

Other procedures using conditions of high stringency would include either a hybridization carried out in 5XSSC, 5X Denhardt's solution, 50% formamide at 42°C for 12 to 48 hours or a washing step carried out in 0.2X SSPE, 0.2% SDS at 65°C for 30 to 60 minutes.

Reagents mentioned in the foregoing procedures for carrying out high stringency hybridization are well known in the art. Details of the composition of these reagents can be found in, *e.g.*, Sambrook, Fritsch, and Maniatis, 1989, Molecular Cloning: A Laboratory Manual, second edition, Cold Spring Harbor Laboratory Press. In addition to the foregoing, other conditions of high stringency which may be used are well known in the art.

The degeneracy of the genetic code is such that, for all but two amino acids, more than a single codon encodes a particular amino acid. This allows for the construction of synthetic DNA that encodes the KCNQ5 protein where the nucleotide

sequence of the synthetic DNA differs significantly from the nucleotide sequences of SEQ.ID.NO:2, but still encodes the same KCNQ5 protein as SEQ.ID.NO:2. Such synthetic DNAs are intended to be within the scope of the present invention.

Mutated forms of SEQ.ID.NO:1 or SEQ.ID.NO:2 are intended to be within the scope of the present invention. In particular, mutated forms of SEQ.ID.NO:1 or SEQ.ID.NO:2 which give rise to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration are within the scope of the present invention.

Another aspect of the present invention includes host cells that have been engineered to contain and/or express DNA sequences encoding KCNQ5 protein. Such recombinant host cells can be cultured under suitable conditions to produce KCNQ5 protein. An expression vector containing DNA encoding KCNQ5 protein can be used for expression of KCNQ5 protein in a recombinant host cell. Recombinant host cells may be prokaryotic or eukaryotic, including but not limited to, bacteria such as *E. coli*, fungal cells such as yeast, mammalian cells including, but not limited to, cell lines of human, bovine, porcine, monkey and rodent origin, amphibian cells such as *Xenopus* oocytes, and insect cells including but not limited to *Drosophila* and silkworm derived cell lines. Cells and cell lines which are suitable for recombinant expression of KCNQ5 protein and which are widely mavailable, include but are not limited to, L cells L-M(TK$^-$) (ATCC CCL 1.3), L cells L-M (ATCC CCL 1.2), 293 (ATCC CRL 1573), Raji (ATCC CCL 86), CV-1 (ATCC CCL 70), COS-1 (ATCC CRL 1650), COS-7 (ATCC CRL 1651), CHO-K1 (ATCC CCL 61), 3T3 (ATCC CCL 92), NIH/3T3 (ATCC CRL 1658), HeLa (ATCC CCL 2), C127I (ATCC CRL 1616), BS-C-1 (ATCC CCL 26), MRC-5 (ATCC CCL 171), ARPE-19 human retinal pigment epithelium (ATCC CRL-2302), *Xenopus* melanophores, and *Xenopus* oocytes.

A variety of mammalian expression vectors can be used to express recombinant KCNQ5 in mammalian cells. Commercially available mammalian expression vectors which are suitable include, but are not limited to, pMC1neo (Stratagene), pSG5 (Stratagene), pcDNAI and pcDNAIamp, pcDNA3, pcDNA3.1, pCR3.1 (Invitrogen), EBO-pSV2-neo (ATCC 37593), pBPV-1(8-2) (ATCC 37110), pdBPV-MMTneo(342-12) (ATCC 37224), pRSVgpt (ATCC 37199), pRSVneo (ATCC 37198), and pSV2-dhfr (ATCC 37146). Another suitable vector is the PT7TS oocyte expression vector. Following expression in recombinant cells, KCNQ5 can

be purified by conventional techniques to a level that is substantially free from other proteins.

Certain voltage-gated potassium channel subunits have been found to require the expression of other voltage-gated potassium channel subunits as "chaperones" in order to be properly expressed at high levels and inserted in membranes. For example, co-expression of KCNQ3 appears to enhance the expression of KCNQ2 in *Xenopus* oocytes (Wang et al., 1998, Science 282:1890-1893). Also, some voltage-gated potassium channel Kv1α subunits require other related alpha subunits or Kvβ2 subunits (Shi et al., 1995, Neuron 16:843-852). Accordingly, the recombinant expression of the KCNQ5 protein may under certain circumstances benefit from the co-expression of other voltage-gated potassium channel proteins and such co-expression is intended to be within the scope of the present invention.

The present invention includes KCNQ5 protein substantially free from other proteins. The amino acid sequence of the full-length KCNQ5 protein is shown in Figure 2 as SEQ.ID.NO.:3. Thus, the present invention includes KCNQ5 protein substantially free from other proteins having the amino acid sequence SEQ.ID.NO.:3. The present invention also includes isolated KCNQ5 protein having the amino acid sequence SEQ.ID.NO.:3.

Mutated forms of KCNQ5 proteins are intended to be within the scope of the present invention. In particular, mutated forms of SEQ.ID.NO:3 that give rise to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration are within the scope of the present invention.

As with many proteins, it is possible to modify many of the amino acids of KCNQ5 and still retain substantially the same biological activity as the original protein. Thus, the present invention includes modified KCNQ5 proteins which have amino acid deletions, additions, or substitutions but that still retain substantially the same biological activity as KCNQ5. It is generally accepted that single amino acid substitutions do not usually alter the biological activity of a protein (see, *e.g.*, Molecular Biology of the Gene, Watson *et al.*, 1987, Fourth Ed., The Benjamin/Cummings Publishing Co., Inc., page 226; and Cunningham & Wells, 1989, Science 244:1081-1085). Accordingly, the present invention includes polypeptides where one amino acid substitution has been made in SEQ.ID.NO:3 wherein the polypeptides still retain substantially the same biological activity as

KCNQ5. The present invention also includes polypeptides where two or more amino acid substitutions have been made in SEQ.ID.NO:3 wherein the polypeptides still retain substantially the same biological activity as KCNQ5. In particular, the present invention includes embodiments where the above-described substitutions are conservative substitutions. In particular, the present invention includes embodiments where the above-described substitutions do not occur in positions where the amino acid present in KCNQ5 is also present in the corresponding position of any one of KCNQ1, KCNQ2, KCNQ3, or KCNQ4 (see Figure 4A-B).

The KCNQ5 proteins of the present invention may contain post-translational modifications, *e.g.*, covalently linked carbohydrate, phosphorylation, myristoylation, *etc.*.

The present invention also includes chimeric KCNQ5 proteins. Chimeric KCNQ5 proteins consist of a contiguous polypeptide sequence of at least a portion of KCNQ5 protein fused to a polypeptide sequence of a non-KCNQ5 protein.

The present invention also includes isolated forms of KCNQ5 proteins and KCNQ5 DNA. Use of the term "isolated" indicates that KCNQ5 protein or KCNQ5 DNA has been removed from its normal cellular environment. Thus, an isolated KCNQ5 protein may be in a cell-free solution or placed in a different cellular environment from that in which it occurs naturally. The term isolated does not imply that an isolated KCNQ5 protein is the only protein present. but instead means that an isolated KCNQ5 protein is at least 95% free of non-amino acid material (*e.g.*, nucleic acids, lipids, carbohydrates) naturally associated with the KCNQ5 protein. Thus, a KCNQ5 protein that is expressed in bacteria or even in eukaryotic cells which do not naturally (*i.e.*, without human intervention) express it through recombinant means is an "isolated KCNQ5 protein."

It is known that other members of the family of potassium channels to which KCNQ5 belongs can interact to form heteromeric structures resulting in functional potassium channels. For example, KCNQ2 and KCNQ3 can assemble to form a heteromeric functional potassium channel (Wang et al., 1998, Science 282:1890-1893). Accordingly, it is believed likely that KCNQ5 will also be able to form heteromeric structures with other proteins where such heteromeric structures constitute functional potassium channels. Thus, the present invention includes such heteromers comprising KCNQ5. Preferred heteromers are those in which KCNQ5 forms heteromers with at least one of KCNQ1, KCNQ2, KCNQ3, or KCNQ4.

A cDNA fragment encoding full-length KCNQ5 can be isolated from a human retinal or brain cDNA library by using the polymerase chain reaction (PCR) employing suitable primer pairs. Such primer pairs can be selected based upon the cDNA sequence for KCNQ5 shown in Figure 2 as SEQ.ID.NO.:2. Suitable primer pairs would be, *e.g.*:

5'-GGGGGCCCGGATGAGCC-3' (SEQ.ID.NO.:9) and

5'-GAAGAACTTATTTCAGTTTGA-3' (SEQ.ID.NO.:10)

The above primers are meant to be illustrative only; one skilled in the art would readily be able to design other suitable primers based upon SEQ.ID.NO.:2. Such primers could be produced by methods of oligonucleotide synthesis that are well known in the art.

PCR reactions can be carried out with a variety of thermostable enzymes including but not limited to AmpliTaq, AmpliTaq Gold, or Vent polymerase. For AmpliTaq, reactions can be carried out in 10 mM Tris-Cl, pH 8.3, 2.0 mM $MgCl_2$, 200 μM for each dNTP, 50 mM KCl, 0.2 μM for each primer, 10 ng of DNA template, 0.05 units/μl of AmpliTaq. The reactions are heated at 95°C for 3 minutes and then cycled 35 times using the cycling parameters of 95°C, 20 seconds, 62°C, 20 seconds, 72°C, 3 minutes. In addition to these conditions, a variety of suitable PCR protocols can be found in PCR Primer, A Laboratory Manual, edited by C.W. Dieffenbach and G.S. Dveksler, 1995, Cold Spring Harbor Laboratory Press; or PCR Protocols: A Guide to Methods and Applications, Michael *et al.*, eds., 1990, Academic Press .

A suitable cDNA library from which a clone encoding KCNQ5 can be isolated would be Human Retina 5'-stretch cDNA library in lambda gt10 or lambda gt11 vectors (catalog numbers HL1143a and HL1132b, Clontech, Palo Alto, CA) or human fetal brain 5-stretch plus cDNA library (catalog number HL5024t, Clontech, Palo Alto, CA). The primary clones of such a library can be subdivided into pools with each pool containing approximately 20,000 clones and each pool can be amplified separately.

By this method, a cDNA fragment encoding an open reading frame of 846 amino acids (SEQ.ID.NO.:3) can be obtained. This cDNA fragment can be cloned into a suitable cloning vector or expression vector. For example, the fragment can be cloned into the mammalian expression vector pcDNA3.1 (Invitrogen, San Diego, CA). KCNQ5 protein can then be produced by transferring an expression

vector encoding KCNQ5 or portions thereof into a suitable host cell and growing the host cell under appropriate conditions. KCNQ5 protein can then be isolated by methods well known in the art.

As an alternative to the above-described PCR method, a cDNA clone encoding KCNQ5 can be isolated from a cDNA library using as a probe oligonucleotides specific for KCNQ5 and methods well known in the art for screening cDNA libraries with oligonucleotide probes. Such methods are described in, *e.g.*, Sambrook *et al.*, 1989, *Molecular Cloning: A Laboratory Manual*; Cold Spring Harbor Laboratory, Cold Spring Harbor, New York; Glover, D.M. (ed.), 1985, *DNA Cloning: A Practical Approach*, MRL Press, Ltd., Oxford, U.K., Vol. I, II. Oligonucleotides that are specific for KCNQ5 and that can be used to screen cDNA libraries can be readily designed based upon the cDNA sequence of KCNQ5 shown in Figure 2 as SEQ.ID.NO.:2 and can be synthesized by methods well-known in the art.

Genomic clones containing the KCNQ5 gene can be obtained from commercially available human PAC or BAC libraries available from Research Genetics, Huntsville, AL. PAC clones containing the KCNQ5 gene (*e.g.*, PAC141B1, PAC224H23) are commercially available from Research Genetics, Huntsville, AL (catalog number for individual PAC clones is RPCI.C). Alternatively, one may prepare genomic libraries, especially in P1 artificial chromosome vectors, from which genomic clones containing the KCNQ5 can be isolated, using probes based upon the KCNQ5 sequences disclosed herein. Methods of preparing such libraries are known in the art (Ioannou *et al.*,1994, Nature Genet. 6:84-89).

The novel DNA sequences of the present invention can be used in various diagnostic methods relating to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. The present invention provides diagnostic methods for determining whether a patient carries a mutation in the KCNQ5 gene that predisposes that patient toward the development of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. In broad terms, such methods comprise determining the DNA sequence of a region of the KCNQ5 gene from the patient and comparing that sequence to the sequence from the corresponding region of the KCNQ5 gene from a non-affected person, *i.e.*, a person who does not suffer from Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration, where a difference in sequence between the DNA sequence of the KCNQ5 gene from the

patient and the DNA sequence of the KCNQ5 gene from the non-affected person indicates that the patient has Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

Such methods of diagnosis may be carried out in a variety of ways. For example, one embodiment comprises:

(a) providing PCR primers from a region of the KCNQ5 gene;

(b) performing PCR on a DNA sample from the patient to produce a PCR fragment from the patient;

(c) performing PCR on a control DNA sample comprising a nucleotide sequence selected from the group consisting of SEQ.ID.NO:1 and SEQ.ID.NO.:2 to produce a control PCR fragment;

(d) determining the nucleotide sequence of the PCR fragment from the patient and the nucleotide sequence of the control PCR fragment;

(e) comparing the nucleotide sequence of the PCR fragment from the patient to the nucleotide sequence of the control PCR fragment;

where a difference between the nucleotide sequence of the PCR fragment from the patient and the nucleotide sequence of the control PCR fragment indicates that the patient has a mutation in the KCNQ5 gene and thus is likely to have Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

In a particular embodiment, the PCR primers are from a region of the KCNQ5 gene where it is suspected that a patient harbors a mutation. In a particular embodiment, the PCR primers are from the coding region of the KCNQ5 gene, *i.e.*, from the coding region of SEQ.ID.NO:1 or SEQ.ID.NO:2. In a particular embodiment, the PCR primers amplify a region that includes the marker D6S280.

In a particular embodiment, the DNA sample from the patient is cDNA that has been prepared from an RNA sample from the patient. In another embodiment, the DNA sample from the patient is genomic DNA. In a particular embodiment, the control DNA sample is DNA from a person who does not have Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

In a particular embodiment, the nucleotide sequences of the PCR fragment from the patient and the control PCR fragment are determined by DNA sequencing.

In a particular embodiment, the nucleotide sequences of the PCR fragment from the patient and the control PCR fragment are compared by direct comparison after DNA sequencing. In another embodiment, step (d) is omitted and the comparison in step (e) is made by a process that includes hybridizing the PCR fragment from the patient and the control PCR fragment and then using an endonuclease that cleaves at any mismatched positions in the hybrid but does not cleave the hybrid if the two fragments match perfectly. Such an endonuclease is, *e.g.*, S1. In this embodiment, the conversion of the PCR fragment from the patient to smaller fragments after endonuclease treatment indicates that the patient carries a mutation in the KCNQ5 gene. In such embodiments, it may be advantageous to label (radioactively, enzymatically, immunologically, *etc.*) the PCR fragment from the patient or the control PCR fragment.

The present invention provides a method of diagnosing whether a patient carries a mutation in the KCNQ5 gene that comprises:

(a) obtaining an RNA sample from the patient;

(b) performing reverse transcription-PCR (RT-PCR) on the RNA sample using primers that span a region of the coding sequence of the KCNQ5 gene to produce a PCR fragment from the patient where the PCR fragment from the patient has a defined length, the length being dependent upon the identity of the primers that were used in the RT-PCR;

(c) hybridizing the PCR fragment to DNA comprising a sequence selected from the group consisting of SEQ.ID.NO:1 and SEQ.ID.NO.:2, or to portions of SEQ.ID.NO:1 or SEQ.ID.NO.:2 that are sufficiently long to give rise to bands that can be seen on polyacrylamide gels, to form a hybrid;

(d) treating the hybrid produced in step (c) with an endonuclease that cleaves at any mismatched positions in the hybrid but does not cleave the hybrid if the two fragments match perfectly;

(e) determining whether the endonuclease cleaved the hybrid by determining the length of the PCR fragment from the patient after endonuclease treatment where a reduction in the length of the PCR fragment from the patient after endonuclease treatment indicates that the patient carries a mutation in the KCNQ5 gene.

In a variation of the above-described method, instead of determining the length of the PCR fragment from the patient after endonuclease treatment, the

length of the DNA comprising a sequence selected from the group consisting of SEQ.ID.NO:1 and SEQ.ID.NO.:2, or the DNA comprising portions of SEQ.ID.NO:1 or SEQ.ID.NO.:2 that are sufficiently long to give rise to bands that can be seen on polyacrylamide gels is determined after endonuclease treatment. In such a variation, a reduction in the length of the DNA comprising a sequence selected from the group consisting of SEQ.ID.NO:1 and SEQ.ID.NO.:2, or the DNA comprising portions of SEQ.ID.NO:1 or SEQ.ID.NO.:2 that are sufficiently long to give rise to bands that can be seen on polyacrylamide gels indicates that the patient carries a mutation in the KCNQ5 gene.

The present invention provides a method of diagnosing whether a patient carries a mutation in the KCNQ5 gene that comprises:

(a) making cDNA from an RNA sample from the patient;

(b) providing a set of PCR primers based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2;

(c) performing PCR on the cDNA to produce a PCR fragment from the patient;

(d) determining the nucleotide sequence of the PCR fragment from the patient;

(e) comparing the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2;

where a difference between the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2 indicates that the patient carries a mutation in the KCNQ5 gene.

The present invention provides a method of diagnosing whether a patient carries a mutation in the KCNQ5 gene that comprises:

(a) preparing genomic DNA from the patient;

(b) providing a set of PCR primers based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2;

(c) performing PCR on the genomic DNA to produce a PCR fragment from the patient;

(d) determining the nucleotide sequence of the PCR fragment from the patient;

(e) comparing the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2;

where a difference between the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2 indicates that the patient carries a mutation in the KCNQ5 gene.

The present invention also provides oligonucleotide probes, based upon the sequences of SEQ.ID.NO:1 or SEQ.ID.NO:2, that can be used in diagnostic methods related to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. In particular, the present invention includes DNA oligonucleotides comprising at least about 10, 15, or 18 contiguous nucleotides of a sequence selected from the group consisting of: SEQ.ID.NO:1 and SEQ.ID.:NO.2 where the oligonucleotide probe comprises no stretch of contiguous nucleotides longer than 5 of a sequence selected from the group consisting of: SEQ.ID.NO:1 and SEQ.ID.:NO.2 other than the said at least about 10, 15, or 18 contiguous nucleotides. The oligonucleotides can be substantially free from other nucleic acids. Also provided by the present invention are corresponding RNA oligonucleotides. The DNA or RNA oligonucleotide probes can be packaged in kits.

In addition to the diagnostic utilities described above, the present invention makes possible the recombinant expression of the KCNQ5 protein in various cell types. Such recombinant expression makes possible the study of this protein so that its biochemical activity and its role in Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration can be elucidated.

The present invention also makes possible the development of assays which measure the biological activity of the KCNQ5 protein. Such assays using recombinantly expressed KCNQ5 protein are especially of interest. Assays for KCNQ5 protein activity can be used to screen libraries of compounds or other sources of compounds to identify compounds that are activators or inhibitors of the activity of KCNQ5 protein. Such identified compounds can serve as "leads" for the development of pharmaceuticals that can be used to treat patients having Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. In versions of the above-described assays, mutant KCNQ5 proteins are used and inhibitors or activators of the activity of the mutant KCNQ5 proteins are identified.

Preferred cell lines for recombinant expression of KCNQ5 are those which do not express endogenous potassium channels (*e.g.*, CV-1, NIH-3T3). Such

cell lines can be loaded with ^{86}Rb, an ion which can pass through potassium channels. The ^{86}Rb-loaded cells can be exposed to collections of substances (*e.g.*, combinatorial libraries, natural products) and those substances that are able to alter ^{86}Rb efflux identified. Such substances are likely to be activators or inhibitors of KCNQ5.

The present invention includes a method of identifying activators or inhibitors of KCNQ5 comprising:

(a) recombinantly expressing KCNQ5 protein or mutant KCNQ5 protein in a host cell;

(b) measuring the biological activity of KCNQ5 protein or mutant KCNQ5 protein in the presence and in the absence of a substance suspected of being an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein;

where a change in the biological activity of the KCNQ5 protein or the mutant KCNQ5 protein in the presence as compared to the absence of the substance indicates that the substance is an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein.

In particular embodiments, the biological activity is the production of a voltage-gated potassium current, or efflux of ^{86}Rb.

In particular embodiments, a vector encoding KCNQ5 is transferred into *Xenopus* oocytes in order to cause the expression of KCNQ5 protein in the oocytes. Alternatively, RNA encoding KCNQ5 protein can be prepared *in vitro* and injected into the oocytes, also resulting in the expression of KCNQ5 protein in the oocytes. Following expression of KCNQ5 in the oocytes, membrane currents are measured after the transmembrane voltage is changed in steps. A change in membrane current is observed when the KCNQ5 channels opens, allowing potassium ion flow. Similar oocytes studies were reported for KCNQ2 and KCNQ3 potassium channels in Wang et al., 1998, Science 282:1890-1893.

Inhibitors of KCNQ5 can be identified by exposing the oocytes expressing KCNQ5 to collections of substances and determining whether the substances can block or diminish the membrane currents observed in the absence of the substance.

Accordingly, the present invention provides a method of identifying inhibitors of KCNQ5 comprising:

(a) expressing KCNQ5 protein in *Xenopus* oocytes;

(b) changing the transmembrane potential of the oocytes in the presence and the absence of a substance suspected of being an inhibitor of KCNQ5;

(c) measuring membrane potassium currents following step (b);

where if the potassium membrane currents measured in step (c) are greater in the absence rather than in the presence of the substance, then the substance is an inhibitor of KCNQ5.

The present invention also includes assays for the identification of activators and inhibitors of KCNQ5 that are based upon FRET between a first and a second fluorescent dye where the first dye is bound to one side of the plasma membrane of a cell expressing KCNQ5 and the second dye is free to shuttle from one face of the membrane to the other face in response to changes in membrane potential. In certain embodiments, the first dye is impenetrable to the plasma membrane of the cells and is bound predominately to the extracellular surface of the plasma membrane. The second dye is trapped within the plasma membrane but is free to diffuse within the membrane. At normal (*i.e.*, negative) resting potentials of the membrane, the second dye is bound predominately to the inner surface of the extracellular face of the plasma membrane, thus placing the second dye in close proximity to the first dye. This close proximity allows for the generation of a large amount of FRET between the two dyes. Following membrane depolarization, the second dye moves from the extracellular face of the membrane to the intracellular face, thus increasing the distance between the dyes. This increased distance results in a decrease in FRET, with a corresponding increase in fluorescent emission derived from the first dye and a corresponding decrease in the fluorescent emission from the second dye. See figure 1 of González & Tsien, 1997, Chemistry & Biology 4:269-277. See also González & Tsien, 1995, Biophys. J. 69:1272-1280 and U.S. Patent No. 5,661,035.

In certain embodiments, the first dye is a fluorescent lectin or a fluorescent phospholipid that acts as the fluorescent donor. Examples of such a first dye are: a coumarin-labeled phosphatidylethanolamine (*e.g.*, N-(6-chloro-7-hydroxy-2-oxo-2H--1-benzopyran-3-carboxamidoacetyl)-dimyristoylphosphatidyl-ethanolamine) or N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-dipalmitoylphosphatidylethanolamine); a fluorescently-labeled lectin (*e.g.*, fluorescein-labeled wheat germ agglutinin). In certain embodiments, the second dye is an oxonol that acts as the fluorescent acceptor. Examples of such a second dye are: bis(1,3-dialkyl-2-thiobarbiturate)trimethineoxonols (*e.g.*, bis(1,3-dihexyl-2-

thiobarbiturate)trimethineoxonol) or pentamethineoxonol analogues (*e.g.*, bis(1,3-dihexyl-2-thiobarbiturate)pentamethineoxonol; or bis(1,3-dibutyl-2-thiobarbiturate)pentamethineoxonol). See González & Tsien, 1997, Chemistry & Biology 4:269-277 for methods of synthesizing various dyes suitable for use in the present invention. In certain embodiments, the assay may comprise a natural carotenoid, *e.g.*, astaxanthin, in order to reduce photodynamic damage due to singlet oxygen.

The above described assays can be utilized to discover activators and inhibitors of KCNQ5. Such assays will generally utilize cells that express KCNQ5, *e.g.*, by transfection with expression vectors encoding KCNQ5. In assays for inhibitors, such cells will generally have a resting membrane potential that is roughly equal to the threshhold for activation of the KCN5Q channel. This is because most untransfected cells will have membrane potentials that are depolarized relative to the threshhold potential of KCNQ5 channels. Therefore, when KCNQ5 is expressed in these cells, the KCNQ5 channels open. This lets K^+ out of the cells, which tends to hyperpolarize the membrane potential. This closes some of the KCNQ5 channels, leading to relative depolarization. In this way, a steady state develops around the threshhold for activation of the KCNQ5 channel. Inhibitors of KCNQ5 will, therefore, disturb this steady state and depolarize the cell. In assays for activators, KCNQ5 will be transfected into a cell line that also expresses a counteracting, depolarizing current. The membrane potential in these cells will therefore be set by contributions of both the KCNQ5 channel and the endogenous depolarizing current, resulting in a more depolarized resting potential. Ideally, the endogenous current will play the major role in the absence of a KCNQ5 activator. Activators of KCNQ5 will open this channel and increase the contribution of KCNQ5 to the membrane potential relative to the other current and the potential will, therefore, hyperpolarize in response to an activator of KCNQ5. Changes in membrane potential (depolarizations and hyperpolarizations) that are caused by activators and inhibitors of KCNQ5 can be monitored by the assays using FRET described above.

Accordingly, the present invention provides a method of identifying activators of KCNQ5 comprising:

(a) providing test cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) exposing the test cells to a substance that is suspected of being an activator of KCNQ5;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

(d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

wherein if the amount of FRET exhibited by the test cells is greater than the amount of FRET exhibited by the control cells, the substance is an activator of KCNQ5;

where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been exposed to the substance.

The present invention also provides a method of identifying inhibitors of KCNQ5 comprising:

(a) providing test cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) exposing the test cells to a substance that is suspected of being an inhibitor of KCNQ5;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

(d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

wherein if the amount of FRET exhibited by the test cells is less than the amount of FRET exhibited by the control cells, the substance is an inhibitor of KCNQ5;

where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been exposed to the substance.

In a variation of the assay described above, instead of the transfected cell's membrane potential being allowed to reach steady state on its own, the membrane potential is artificially set at a potential in which the KCNQ5 channel is open. This can be done, *e.g.*, by variation of the external K^+ concentration in a known manner (*e.g.*, increased concentrations of external K^+). If such cells, having open KCNQ5 channels, are exposed to inhibitors of KCNQ5, the KCNQ5 channels will close, and the cells' membrane potentials will be depolarized. This depolarization can be observed as a decrease in FRET.

Accordingly, the present invention provides a method of identifying inhibitors of KCNQ5 comprising:

(a) providing cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) adjusting the membrane potential of the cells such that the ion channel formed by KCNQ5 is open;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells;

(d) repeating step (b) and step (c) while the cells are exposed to a substance that is suspected of being an inhibitor of KCNQ5;

where if the amount of FRET exhibited by the cells that are exposed to the substance is less than the amount of FRET exhibited by the cells that have not been exposed to the substance, then the substance is an inhibitor of KCNQ5.

In particular embodiments of the above-described methods, the expression vectors are transfected into the test cells.

In particular embodiments of the above-described methods, KCNQ5 has an amino acid sequence of SEQ.ID.NO.:3.

In particular embodiments of the above-described methods, the first fluorescent dye is selected from the group consisting of: a fluorescent lectin; a fluorescent phospholipid; a coumarin-labeled phosphatidylethanolamine; N-(6-chloro-7-hydroxy-2-oxo-2H--1-benzopyran-3-carboxamidoacetyl)-dimyristoylphosphatidyl-ethanolamine); N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-dipalmitoylphosphatidylethanolamine); and fluorescein-labeled wheat germ agglutinin.

In particular embodiments of the above-described methods, the second fluorescent dye is selected from the group consisting of: an oxonol that acts as the fluorescent acceptor; bis(1,3-dialkyl-2-thiobarbiturate)trimethineoxonols; bis(1,3-dihexyl-2-thiobarbiturate)trimethineoxonol; bis(1,3-dialkyl-2-thiobarbiturate)quatramethineoxonols; bis(1,3-dialkyl-2-thiobarbiturate)pentamethineoxonols; bis(1,3-dihexyl-2-thiobarbiturate)pentamethineoxonol; bis(1,3-dibutyl-2-thiobarbiturate)pentamethineoxonol); and bis(1,3-dialkyl-2-thiobarbiturate)hexamethineoxonols.

In a particular embodiment of the above-described methods, the cells are eukaryotic cells. In another embodiment, the cells are mammalian cells. In other embodiments, the cells are L cells L-M(TK$^-$) (ATCC CCL 1.3), L cells L-M (ATCC CCL 1.2), 293 (ATCC CRL 1573), Raji (ATCC CCL 86), CV-1 (ATCC CCL 70), COS-1 (ATCC CRL 1650), COS-7 (ATCC CRL 1651), CHO-K1 (ATCC CCL 61), 3T3 (ATCC CCL 92), NIH/3T3 (ATCC CRL 1658), HeLa (ATCC CCL 2), C127I (ATCC CRL 1616), BS-C-1 (ATCC CCL 26), MRC-5 (ATCC CCL 171), *Xenopus* melanophores, or *Xenopus* oocytes.

In particular embodiments of the above-described methods, the control cells do not comprise item (a)(1) but do comprise items (a)(2) and (a)(3).

In assays to identify activators or inhibitors of KCNQ5, it may be advantageous to co-express another potassium channel, *e.g.*, KCNQ1, KCNQ2, KCNQ3, or KCNQ4, together with KCNQ5, or with an accessory subunit, such as the IsK protein or one of its homologues, in order to form a functional heteromeric potassium channel.

While the above-described methods are explicitly directed to testing whether "a" substance is an activator or inhibitor of KCNQ5, it will be clear to one skilled in the art that such methods can be adapted to test collections of substances, *e.g.*, combinatorial libraries, to determine whether any members of such collections are activators or inhibitors of KCNQ5. Accordingly, the use of collections of substances, or individual members of such collections, as the substance in the above-described methods is within the scope of the present invention.

The present invention includes pharmaceutical compositions comprising activators or inhibitors of KCNQ5 protein that have been identified by the herein-described methods. The activators or inhibitors are generally combined with pharmaceutically acceptable carriers to form pharmaceutical compositions. Examples of such carriers and methods of formulation of pharmaceutical compositions containing activators or inhibitors and carriers can be found in Remington's Pharmaceutical Sciences. To form a pharmaceutically acceptable composition suitable for effective administration, such compositions will contain a therapeutically effective amount of the activators or inhibitors.

Therapeutic or prophylactic compositions are administered to an individual in amounts sufficient to treat or prevent conditions where KCNQ5 activity is abnormal. The effective amount can vary according to a variety of factors such as the individual's condition, weight, gender, and age. Other factors include the mode of administration. The appropriate amount can be determined by a skilled physician.

Compositions can be used alone at appropriate dosages. Alternatively, co-administration or sequential administration of other agents can be desirable.

The compositions can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for administration. For example, the compositions can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, solutions, suspensions, syrups and emulsions, or by injection. Likewise, they can also be administered in intravenous (both bolus and infusion),

intraperitoneal, subcutaneous, topical with or without occlusion, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

Advantageously, compositions can be administered in a single daily dose, or the total daily dosage can be administered in divided doses of two, three or four times daily. Furthermore, compositions can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The dosage regimen utilizing the compositions is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal, hepatic and cardiovascular function of the patient; and the particular composition thereof employed. A physician of ordinary skill can readily determine and prescribe the effective amount of the composition required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentrations of composition within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the composition's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a composition.

The present invention includes a method of treating Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, age-related macular degeneration and other forms of macular degeneration, deafness, epilepsy, and different forms of neuropsychiatric, heart, gastrointestinal, and muscle disorders by administering to a patient a therapeutically effective amount of a substance that is an activator or an inhibitor of a voltage-gated potassium channel containing the KCNQ5 protein.

When screening compounds in order to identify potential pharmaceuticals that specifically interact with a target ion channel, it is necessary to ensure that the compounds identified are as specific as possible for the target ion channel. To do this, it is necessary to screen the compounds against as wide an array as possible of ion channels that are similar to the target ion channel. Thus, in order to find compounds that are potential pharmaceuticals that interact with ion channel A, it

is not enough to ensure that the compounds interact with ion channel A (the "plus target") and produce the desired pharmacological effect through ion channel A. It is also necessary to determine that the compounds do not interact with ion channels B, C, D, *etc* .(the "minus targets"). In general, as part of a screening program, it is important to have as many minus targets as possible (see Hodgson, 1992, Bio/Technology 10:973-980, at 980). KCNQ5 protein, DNA encoding KCNQ5 protein, and recombinant cells that have been engineered to express KCNQ5 protein have utility in that they can be used as "minus targets" in screens designed to identify compounds that specifically interact with other ion channels. For example, Wang et al., 1998, Science 282:1890-1893 have shown that KCNQ2 and KCNQ3 form a heteromeric potassium ion channel know as the "M-channel." The M-channel is an important target for drug discovery since mutations in KCNQ2 and KCNQ3 are responsible for causing epilepsy (Biervert et al., 1998, Science 279:403-406; Singh et al., 1998, Nature Genet. 18:25-29; Schroeder et al., Nature 1998, 396:687-690). A screening program designed to identify activators or inhibitors of the M-channel would benefit greatly by the use of KCNQ5 as a minus target.

The present invention also includes antibodies to the KCNQ5 protein. Such antibodies may be polyclonal antibodies or monoclonal antibodies. The antibodies of the present invention are raised against the entire KCNQ5 protein or against suitable antigenic fragments of the protein that are coupled to suitable carriers, *e.g.*, serum albumin or keyhole limpet hemocyanin, by methods well known in the art. Methods of identifying suitable antigenic fragments of a protein are known in the art. See, *e.g.*, Hopp & Woods, 1981, Proc. Natl. Acad. Sci. USA 78:3824-3828; and Jameson & Wolf, 1988, CABIOS (Computer Applications in the Biosciences) 4:181-186.

For the production of polyclonal antibodies, KCNQ5 protein or an antigenic fragment, coupled to a suitable carrier, is injected on a periodic basis into an appropriate non-human host animal such as, *e.g.*, rabbits, sheep, goats, rats, mice. The animals are bled periodically and sera obtained are tested for the presence of antibodies to the injected antigen. The injections can be intramuscular, intraperitoneal, subcutaneous, and the like, and can be accompanied with adjuvant.

For the production of monoclonal antibodies, KCNQ5 protein or an antigenic fragment, coupled to a suitable carrier, is injected into an appropriate non-human host animal as above for the production of polyclonal antibodies. In the case

of monoclonal antibodies, the animal is generally a mouse. The animal's spleen cells are then immortalized, often by fusion with a myeloma cell, as described in Kohler & Milstein, 1975, Nature 256:495-497. For a fuller description of the production of monoclonal antibodies, see Antibodies: A Laboratory Manual, Harlow & Lane, eds., Cold Spring Harbor Laboratory Press, 1988.

Gene therapy may be used to introduce KCNQ5 polypeptides into the cells of target organs, *e.g.*, the pigmented epithelium of the retina or other parts of the retina. Nucleotides encoding KCNQ5 polypeptides can be ligated into viral vectors which mediate transfer of the nucleotides by infection of recipient cells. Suitable viral vectors include retrovirus, adenovirus, adeno-associated virus, herpes virus, vaccinia virus, lentivirus, and polio virus based vectors. Alternatively, nucleotides encoding KCNQ5 polypeptides can be transferred into cells for gene therapy by non-viral techniques including receptor-mediated targeted transfer using ligand-nucleotide conjugates, lipofection, membrane fusion, or direct microinjection. These procedures and variations thereof are suitable for *ex vivo* as well as *in vivo* gene therapy. Gene therapy with KCNQ5 polypeptides will be particularly useful for the treatment of diseases where it is beneficial to elevate KCNQ5 activity.

The present invention includes processes for cloning orthologues of human KCNQ5 from non-human species. In general, such processes include preparing a PCR primer or a hybridization probe based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2 that can be used to amplify a fragment containing the non-human KCNQ5 (in the case of PCR) from a suitable DNA preparation or to select a cDNA or genomic clone containing the non-human KCNQ5 from a suitable library. A preferred embodiment of this process is a process for cloning the KCNQ5 gene from mouse.

By providing DNA encoding mouse KCNQ5, the present invention allows for the generation of an animal model of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. Such animal models can be generated by making transgenic "knockout" or "knockin" mice containing altered KCNQ5 genes. Knockout mice can be generated in which portions of the mouse KCNQ5 gene have been deleted. Knockin mice can be generated in which mutations that have been shown to lead to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration when present in the human KCNQ5 gene are introduced into the mouse gene. Such knockout and

knockin mice will be valuable tools in the study of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration and will provide important model systems in which to test potential pharmaceuticals or treatments for Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

Accordingly, the present invention includes a method of producing a mouse model of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration comprising:

(a) designing PCR primers or an oligonucleotide probe based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2 for use in cloning the mouse KCNQ5 gene;

(b) using the PCR primers or the oligonucleotide probe to clone at least a portion of the mouse KCNQ5 gene, the portion being large enough to use in making a transgenic mouse;

(c) producing a transgenic mouse having at least one copy of the mouse KCNQ5 gene altered from its native state.

Methods of producing knockout and knockin mice are well known in the art. One method involves the use of gene-targeted ES cells in the generation of gene-targeted transgenic knockout mice and is described in, *e.g.*, Thomas et al., 1987, Cell 51:503-512, and is reviewed elsewhere (Frohman et al., 1989, Cell 56:145-147; Capecchi, 1989, Trends in Genet. 5:70-76; Baribault et al., 1989, Mol. Biol. Med. 6:481-492).

Techniques are available to inactivate or alter any genetic region to virtually any mutation desired by using targeted homologous recombination to insert specific changes into chromosomal genes. Generally, use is made of a "targeting vector," *i.e.*, a plasmid containing part of the genetic region it is desired to mutate. By virtue of the homology between this part of the genetic region on the plasmid and the corresponding genetic region on the chromosome, homologous recombination can be used to insert the plasmid into the genetic region, thus disrupting the genetic region. Usually, the targeting vector contains a selectable marker gene as well.

In comparison with homologous extrachromosomal recombination, which occurs at frequencies approaching 100%, homologous plasmid-chromosome recombination was originally reported to only be detected at frequencies between 10^{-6} and 10^{-3} (Lin et al., 1985, Proc. Natl. Acad. Sci. USA 82:1391-1395; Smithies et al., 1985, Nature 317: 230-234; Thomas et al., 1986, Cell 44:419-428).

Nonhomologous plasmid-chromosome interactions are more frequent, occurring at levels 10^5-fold (Lin et al., 1985, Proc. Natl. Acad. Sci. USA 82:1391-1395) to 10^2-fold (Thomas et al., 1986, Cell 44:419-428) greater than comparable homologous insertion.

To overcome this low proportion of targeted recombination in murine ES cells, various strategies have been developed to detect or select rare homologous recombinants. One approach for detecting homologous alteration events uses the polymerase chain reaction (PCR) to screen pools of transformant cells for homologous insertion, followed by screening individual clones (Kim et al., 1988, Nucleic Acids Res. 16:8887-8903; Kim et al., 1991, Gene 103:227-233). Alternatively, a positive genetic selection approach has been developed in which a marker gene is constructed which will only be active if homologous insertion occurs, allowing these recombinants to be selected directly (Sedivy et al., 1989, Proc. Natl. Acad. Sci. USA 86:227-231). One of the most powerful approaches developed for selecting homologous recombinants is the positive-negative selection (PNS) method developed for genes for which no direct selection of the alteration exists (Mansour et al., 1988, Nature 336:348-352; Capecchi, 1989, Science 244:1288-1292; Capecchi, 1989, Trends in Genet. 5:70-76). The PNS method is more efficient for targeting genes which are not expressed at high levels because the marker gene has its own promoter. Nonhomologous recombinants are selected against by using the Herpes Simplex virus thymidine kinase (HSV-TK) gene and selecting against its nonhomologous insertion with herpes drugs such as gancyclovir (GANC) or FIAU (1-(2-deoxy 2-fluoro-B-D-arabinofluranosyl)-5-iodouracil). By this counter-selection, the percentage of homologous recombinants in the surviving transformants can be increased.

Other methods of producing transgenic mice involve microinjecting the male pronuclei of fertilized eggs. Such methods are well known in the art.

The following non-limiting examples are presented to better illustrate the invention.

EXAMPLE 1

Identification of the human KCNQ5 gene and cDNA cloning

Construction of Libraries for Shotgun Sequencing from PAC Clones

Bacterial strains containing the KCNQ5 PACs (P1 Artificial Chromosomes) were received from Research Genetics (Huntsville, AL). Cells were streaked on Luria-Bertani (LB) agar plates supplemented with the appropriate antibiotic. A single colony was used to prepare a 5-ml starter culture and then 1-L overnight culture in LB medium. The cells were pelleted by centrifugation and PAC DNA was purified by equilibrium centrifugation in cesium chloride-ethidium bromide gradient (Sambrook, Fritsch, and Maniatis, 1989, Molecular Cloning: A Laboratory Manual, second edition, Cold Spring Harbor Laboratory Press). Purified PAC DNA was brought to 50 mM Tris pH 8.0, 15 mM $MgCl_2$, and 25% glycerol in a volume of 2 ml and placed in a AERO-MIST nebulizer (CIS-US, Bedford, MA). The nebulizer was attached to a nitrogen gas source and the DNA was randomly sheared at 10 psi for 30 sec. The sheared DNA was ethanol precipitated and resuspended in TE (10 mM Tris, 1 mM EDTA). The ends were made blunt by treatment with Mung Bean Nuclease (Promega, Madison, WI) at 30°C for 30 min, followed by phenol/chloroform extraction, and treatment with T4 DNA polymerase (GIBCO/BRL, Gaithersburg, MD) in multicore buffer (Promega, Madison, WI) in the presence of 40 uM dNTPs at 16°C. To facilitate subcloning of the DNA fragments, BstX I adapters (Invitrogen, Carlsbad, CA) were ligated to the fragments at 14°C overnight with T4 DNA ligase (Promega, Madison, WI). Adapters and DNA fragments less than 500 bp were removed by column chromatography using a cDNA sizing column (GIBCO/BRL, Gaithersburg, MD) according to the instructions provided by the manufacturer. Fractions containing DNA greater than 1 kb were pooled and concentrated by ethanol precipitation. The DNA fragments containing BstX I adapters were ligated into the BstX I sites of pSHOT II which was constructed by subcloning the BstX I sites from pcDNA II (Invitrogen, Carlsbad, CA) into the BssH II sites of pBlueScript (Stratagene, La Jolla, CA). pSHOT II was prepared by digestion with BstX I restriction endonuclease and purified by agarose gel electrophoresis. The gel purified vector DNA was extracted from the agarose by following the Prep-A-Gene (BioRad, Richmond, CA) protocol. To reduce ligation of

the vector to itself, the digested vector was treated with calf intestinal phosphatase (GIBCO/BRL, Gaithersburg, MD. Ligation reactions of the DNA fragments with the cloning vector were transformed into ultra-competent XL-2 Blue cells (Stratagene, La Jolla, CA), and plated on LB agar plates supplemented with 100 µg/ml ampicillin. Individual colonies were picked into a 96 well plate containing 100 µl/well of LB broth supplemented with ampicillin and grown overnight at 37°C. Approximately 25 µl of 80% sterile glycerol was added to each well and the cultures stored at -80°C.

Preparation of plasmid DNA

Glycerol stocks were used to inoculate 5 ml of LB broth supplemented with 100 µg/ml ampicillin either manually or by using a Tecan Genesis RSP 150 robot (Tecan AG, Hombrechtikon, Switzerland) programmed to inoculate 96 tubes containing 5 ml broth from the 96 wells. The cultures were grown overnight at 37°C with shaking to provide aeration. Bacterial cells were pelleted by centrifugation , the supernatant decanted, and the cell pellet stored at -20°C. Plasmid DNA was prepared with a QIAGEN Bio Robot 9600 (QIAGEN, Chatsworth, CA) according to the Qiawell Ultra protocol. To test the frequency and size of inserts, plasmid DNA was digested with the restriction endonuclease Pvu II. The size of the restriction endonuclease products was examined by agarose gel electrophoresis with the average insert size being 1 to 2 kb.

DNA Sequence Analysis of Shotgun clones

DNA sequence analysis was performed using the ABI PRISM™ dye terminator cycle sequencing ready reaction kit with AmpliTaq DNA polymerase, FS (Perkin Elmer, Norwalk, CT). DNA sequence analysis was performed with M13 forward and reverse primers. Following amplification in a Perkin-Elmer 9600, the extension products were purified and analyzed on an ABI PRISM 377 automated sequencer (Perkin Elmer, Norwalk, CT). Approximately 4 sequencing reactions were performed per kb of DNA to be examined (384 sequencing reactions per each of nine PACs).

Assembly of DNA sequences

Phred/Phrap was used for DNA sequences assembly. This program was developed by Dr. Phil Green and licensed from the University of Washington

(Seattle, WA). Phred/Phrap consists of the following programs: Phred for base-calling, Phrap for sequence assembly, Crossmatch for sequence comparisons, Consed and Phrapview for visualization of data, Repeatmasker for screening repetitive sequences. Vector and *E. coli* DNA sequences were identified by Crossmatch and removed from the DNA sequence assembly process. DNA sequence assembly was on a SUN Enterprise 4000 server running a Solaris 2.51 operating system (Sun Microsystems Inc., Mountain View, CA) using default Phrap parameters. The sequence assemblies were further analyzed using Consed and Phrapview.

Genomic sequence of the KCNQ5 gene and its exon/intron organization

Genomic DNA sequence from PAC 141B1 was compared with GenBank database entries using the BLASTN and BLASTX algorithms of the AceDB package. This comparison originally revealed a total of 5 exons (exons 3(D), 4 (A), 5(B), 6(E), and 7(C) delineated in Figure1), based on their homology to the known potassium channel genes KCNQ1, KCNQ2, KCNQ3, and KCNQ4. Full-length cDNA was rescued from the pools of the human fetal brain cDNA library using the RCCA technique described in Example 2. Comparison of the cDNA sequence and genomic sequence of PAC141B1 revealed a total of 8 exons (exons 3-10 delineated in Figure1). Genomic regions corresponding to exons 1,2, and 11-14 were not present in PAC141B1.

In order to identify the genomic region corresponding to exon 2 and its right flanking intron, oligonucleotide KCN-2L2 (TTTTCTCCTTGTCTTTGGTTGCTTG; SEQ.ID.NO.:11) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-2L1 (CCTCAAGTTGCCTCTTGATCCTG; SEQ.ID.NO.:13) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 2 and its left flanking intron, oligonucleotide KCN-2R1 (CAGGATCAAGAGGCAACTTGAGG; SEQ.ID.NO.:15) from the KCNQ5 cDNA in combination with the adaptor primer AP1

(CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-2R2 (CCAATTTTGTGTGCTCAGGGATGGTAGA; SEQ.ID.NO.:16) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 11 and its right flanking intron, oligonucleotide KCN-11L1 (GACACAGCCCTTGGCACT; SEQ.ID.NO.:17) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-11L2 (GATGATGTATATGATGAAAAAGGATG; SEQ.ID.NO.:18) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 11 and its left flanking intron, oligonucleotide KCN-11R1 (CTGATAGCTCGAATGACAGTTTT; SEQ.ID.NO.:19) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN11-R2 (AAGTGGTGGGGTGAGGTCTTCCACTG; SEQ.ID.NO.:20) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 12 and its right flanking intron, oligonucleotide KCN-12L1 (AGA ATT ATG AAA TTT CAT GTT GCA; SEQ.ID.NO.:21) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-12L2 (AAA CGG AAG TTT AAG GAA ACA TT; SEQ.ID.NO.:22) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 12 and its left flanking intron, oligonucleotide KCN-12R1 (ACG TGT TTG TTG GCT TTT AAT TC; SEQ.ID.NO.:23) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-12R2 (TAC ACA ACA TGT CCA GAT GAC; SEQ.ID.NO.:24) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 13 and its right flanking intron, oligonucleotide KCN-13L1 (TGATCAAATTCTTGGAAAAGGG; SEQ.ID.NO.:25) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-13L2 (TCACATCAGATAAGAAGAGCCGA; SEQ.ID.NO.:26) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 13 and its left flanking intron, oligonucleotide KCN-13R1 (GTTTTTCAACCTTGACCACCC; SEQ.ID.NO.:27) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-13R2 (AGCATACTGAGATCGTCTGTGGT; SEQ.ID.NO.:28) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 14 and its left flanking intron, oligonucleotide KCN-2543R(AATTCCAAAAGTGTCTGTCTCTGTC; SEQ.ID.NO.:29) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-

amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-2512R (GGACCCACCTCTTCATCAGTTA; SEQ.ID.NO.:30) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

Products obtained from these PCR amplifications were analyzed using ABI 377 sequencers according to standard protocols. Comparison of the full-length KCNQ5 cDNA sequence with the sequences of PAC141B1and sequences obtained in PCR reactions with DNA from the GenomeWalker kit revealed all 14 exons of the KCNQ5 gene. Exact sequence of exon/intron boundaries within the KCNQ5 gene were determined for exons 2-14. The splice signals in all introns conform to published consensus sequences.

EXAMPLE 2

Cloning of KCNQ5 cDNA

The DNA sequence of the cDNA fragment that matches exons 3(D), 4 (A), 5(B), 6(E), and 7(C) of the KCNQ5 was deduced from the genomic sequence of PAC 141B1. Subsequent sequencing of PCR fragments obtained in RCCA reactions confirmed the presence of this fragment in the cDNA library from human fetal brain. This original cDNA fragment corresponds to the cDNA region with coordinates 368-1,004 in Figure 2.

A PCR based technique termed Reduced Complexity cDNA Analysis (RCCA) was used to extend this original cDNA fragment. RCCA is similar to procedures reported by Munroe et al., 1995, Proc. Natl. Acad. Sci. USA 92: 2209-2213 and Wilfinger et al., 1997, BioTechniques 22:481-486 and relies upon a PCR template that is a pool of approximately 20,000 cDNA clones; this reduces the complexity of the template and increases the probability of obtaining longer PCR extensions.

96 wells of a human fetal brain plasmid library were scanned, 20,000 clones per well, by amplifying a 483 bp PCR product using primers KCN-DL (GGAAGACTGAGGTTTGCTCG; SEQ.ID.NO.31) and KCN-ER (GGCAGGAAGTGCAAAGAAAG; SEQ.ID.NO.32). Eight wells were found to

contain the correct 483 bp fragment by PCR analysis. 5' and 3' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers , PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F (CCCAGGCTTTACACTTTATGCTTCC; SEQ.ID.NO.34) were both used in combination with gene specific primers KCN-DL and KCN-ER because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R (CCAGGGTTTTCCCAGTCACGAC; SEQ.ID.NO.35) and PBS 838F (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primers KCN-EL (CTTTCTTTGCACTTCCTGCC; SEQ.ID.NO.37) and KCN-DR1 (AACACAGAAGGGCTTTCGAG; SEQ.ID.NO.38). The PCR products were separated from the unincorporated dNTP's and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 30 µl of water. The products were analyzed on ABI 377 sequencers according to standard protocols.

PCR fragments were assembled into a contig termed "KCN consensus 2_16_99" that corresponds to the cDNA region with coordinates 278-1,456 in Figure 2. A second round of the RCCA analysis was performed to obtain the clones extending to the 3' end of the cDNA contig termed "KCN consensus 2_16_99". 96 wells of a human fetal brain plasmid library were scanned, 20,000 clones per well, by amplifying a 117 bp PCR product using primers KCN-11L1 (GACACAGCCCTTGGCACT; SEQ.ID.NO.17) and KCN-11R1 (CTGATAGCTCGAATGACAGTTTT; SEQ.ID.NO.19) that were derived from the 3' sequence of the cDNA contig termed "KCN consensus 2_16_99". A number of wells were found to contain the correct 117 bp fragment by PCR analysis. 3' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers, PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F (CCCAGGCTTTACACTTTATGCTTCC; SEQ.ID.NO.34) were both used in combination with gene specific primer KCN-11L1 (GACACAGCCCTTGGCACT; SEQ.ID.NO.17) because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R (CCAGGGTTTTCCCAGTCACGAC; SEQ.ID.NO.35) and PBS 838F (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primer

KCN11-R2 (AAGTGGTGGGGTGAGGTCTTCCACTG; SEQ.ID.NO.20). The PCR products were separated from the unincorporated dNTPs and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 30 µl of water. The products were analyzed on ABI 377 sequencers according to standard protocols.

PCR fragments were assembled into a contig termed "KCN consensus 2_26_99" that corresponds to the cDNA region with coordinates 278-2,527 in Figure 2. A third round of RCCA analysis was performed to obtain the clones extending to the 5' end of the cDNA contig termed "KCN consensus 2_26_99". 96 wells of a human fetal brain plasmid library were scanned, 20,000 clones per well, by amplifying a 214 bp PCR product using primers KCN-2L2 (TTTTCTCCTTGTCTTTGGTTGCTTG; SEQ.ID.NO.11) and KCN-DR1 (AACACAGAAGGGCTTTCGAG; SEQ.ID.NO.38) that were derived from the 5' sequence of the cDNA contig termed "KCN consensus 2_26_99". A number of wells were found to contain the correct 214 bp fragment by PCR analysis. 5' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers, PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F (CCCAGGCTTTACACTTTATGCTTCC; SEQ.ID.NO.34) were both used in combination with gene specific primer KCN-DR1 (AACACAGAAGGGCTTTCGAG; SEQ.ID.NO.38) because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R (CCAGGGTTTTCCCAGTCACGAC; SEQ.ID.NO.35) and PBS 838F (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primer KCN-DR2 (CAGTCTTCCTTGCCATCCTC; SEQ.ID.NO.39). The PCR products were separated from the unincorporated dNTPs and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 30 µl of water. The products were analyzed on ABI 377 sequencers according to standard protocols.

PCR fragments were assembled into a contig termed "KCN consensus 3_3_99" that corresponds to the cDNA region with coordinates 1-2,527 in Figure 2. A fourth round of RCCA analysis was performed to obtain the clones extending to the 3' end of the cDNA contig termed "KCN consensus 3_3_99". 96 wells of a human

fetal brain plasmid library were scanned, 20,000 clones per well, by amplifying a 145 bp PCR product using primers KCN-2106L (GCAGCCCCAACAACTTTACA; SEQ.ID.NO.40) and KCN-2250R (CATTTTCCTTGGAGGCAACA; SEQ.ID.NO.41) that were derived from the 3' sequence of the cDNA contig termed "KCN consensus 3_3_99". A number of wells were found to contain the correct 214 bp fragment by PCR analysis. 5' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers , PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F (CCCAGGCTTTACACTTTATGCTTCC; SEQ.ID.NO.34) were both used in combination with gene specific primer KCN-2106L (GCAGCCCCAACAACTTTACA; SEQ.ID.NO.40) because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R (CCAGGGTTTTCCCAGTCACGAC; SEQ.ID.NO.35) and PBS 838F (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primer KCN-2165L (GCCAGAAACTCTGCACCCTA; SEQ.ID.NO.42). The PCR products were separated from the unincorporated dNTP's and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 30 µl of water. The products were analyzed on ABI 377 sequencers according to standard protocols; PCR fragments were assembled into a contig termed "KCN consensus 3_15_99" that corresponds to the cDNA sequence depicted in Figure 2.

EXAMPLE 3

Analysis of expression of KCNQ5

RT-PCR: RT-PCR experiments were performed on "quick-clone" human cDNA samples available from Clontech, Palo Alto, CA. cDNA samples from heart, brain, placenta, lung, liver, skeletal muscle, kidney, pancreas, and retina were amplified with primers KCN-DL (GGAAGACTGAGGTTTGCTCG; SEQ.ID.NO.31) and KCN-ER (GGCAGGAAGTGCAAAGAAAG; SEQ.ID.NO.32) in the following PCR conditions:

1.	94°C	10 min
2.	94°C	30 sec
3.	72°C	2 min (decrease this temperature by 1.1°C per cycle)
4.	72°C	2 min
5.	Go	to step 2 21 more times
6.	94°C	30 sec
7.	55°C	2 min
8.	72°C	2 min
9.	Go to step 6 19 more times	
10.	72°C	7 min
11.	4°C	

The KCNQ5 gene was found to be predominantly expressed in human retina and brain (Figure 3B).

Northern blot analysis: Northern blots containing poly(A+)-RNA from human heart, brain, placenta, lung, liver, skeletal muscle, kidney, pancreas were purchased from Clontech, Palo Alto, CA. Primers KCN-DL (GGAAGACTGAGGTTTGCTCG; SEQ.ID.NO.31) and KCN-ER (GGCAGGAAGTGCAAAGAAAG; SEQ.ID.NO.32) were used to amplify a PCR product of 483 bp from a quick-clone human retina cDNA available from Clontech, Palo Alto, CA. This fragment was purified on an agarose gel, the DNA extracted and used as a probe for Northern blot hybridization.

The probe was labeled by random priming with the Amersham Rediprime kit (Arlington Heights, IL) in the presence of 50-100 μCi of 3000 Ci/mmole [alpha ^{32}P]dCTP (Dupont/NEN, Boston, MA). Unincorporated nucleotides were removed with a ProbeQuant G-50 spin column (Pharmacia/Biotech, Piscataway, NJ). The radiolabeled probe at a concentration of greater than 1 x 10^6 cpm/ml in rapid hybridization buffer (Clontech, Palo Alto, CA) was incubated overnight at 65°C. The blots were washed by two 15 min incubations in 2X SSC, 0.1% SDS (prepared from 20X SSC and 20 % SDS stock solutions, Fisher, Pittsburgh, PA) at room temperature, followed by two 15 min incubations in 1X SSC, 0.1% SDS at room temperature, and two 30 min incubations in 0.1X SSC, 0.1% SDS

at 60°C. Autoradiography of the blots was done to visualize the bands that specifically hybridized to the radiolabeled probe.

The probe hybridized to an mRNA transcript that is predominately expressed in brain and retina (Figure 3A).

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

WHAT IS CLAIMED IS:

1. An isolated DNA comprising nucleotides encoding a KCNQ5 protein.

2. The DNA of claim 1 comprising nucleotides encoding a polypeptide having the amino acid sequence SEQ.ID.NO.:3.

3. The DNA of claim 1 comprising a nucleotide sequence selected from the group consisting of: SEQ.ID.NO.:1, SEQ.ID.NO.:2, and positions 138-2,675 of SEQ.ID.NO.:2.

4. An isolated DNA that hybridizes under stringent conditions to a nucleotide sequence selected from the group consisting of: SEQ.ID.NO.:1 and SEQ.ID.NO.:2.

5. An expression vector comprising the DNA of claim 1.

6. A recombinant host cell comprising the DNA of claim 1.

7. An isolated KCNQ5 protein.

8. The KCNQ5 protein of claim 7 having the amino acid sequence SEQ.ID.NO.: 3.

9. The KCNQ5 protein of claim 8 containing a single amino acid substitution.

10. The KCNQ5 protein of claim 8 containing two or more amino acid substitutions where the amino acid substitutions do not occur in a position where the amino acid substituted in KCNQ5 is also present in the corresponding position of any one of KCNQ2, KCNQ3, or KCNQ4.

11. An antibody that binds specifically to a KCNQ5 protein where the KCNQ5 protein has the amino acid sequence SEQ.ID.NO.:3.

12. A method of diagnosing whether a patient has Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration that comprises determining the DNA sequence of a region of the KCNQ5 gene from the patient and comparing that sequence to the sequence from the corresponding region of the KCNQ5 gene from a non-affected person, *i.e.*, a person who does not have Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration, where a difference in sequence between the DNA sequence of the KCNQ5 gene from the patient and the DNA sequence of the KCNQ5 gene from the non-affected person indicates that the patient has Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

13. A method of diagnosing whether a patient carries a mutation in the KCNQ5 gene that comprises:

(a) providing a DNA sample from the patient;

(b) providing a set of PCR primers based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2;

(c) performing PCR on the DNA sample to produce a PCR fragment from the patient;

(d) determining the nucleotide sequence of the PCR fragment from the patient;

(e) comparing the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2;

where a difference between the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2 indicates that the patient carries a mutation in the KCNQ5 gene.

14. The method of claim 13 where the DNA sample is genomic DNA.

15. The method of claim 13 where the DNA sample is cDNA.

16. A DNA or RNA oligonucleotide probe comprising at least 18 contiguous nucleotides of at least one of a sequence selected from the group consisting of: SEQ.ID.NO.:1 and SEQ.ID.NO.:2.

17. A method for determining whether a substance is an activator or an inhibitor of a KCNQ5 protein or a mutant KCNQ5 protein comprising:

(a) recombinantly expressing KCNQ5 protein or mutant KCNQ5 protein in a host cell;

(b) measuring the biological activity of KCNQ5 protein or mutant KCNQ5 protein in the presence and in the absence of a substance suspected of being an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein;

where a change in the biological activity of the KCNQ5 protein or the mutant KCNQ5 protein in the presence as compared to the absence of the substance indicates that the substance is an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein.

18. A method of identifying inhibitors of KCNQ5 comprising:

(a) expressing KCNQ5 protein in *Xenopus* oocytes;

(b) changing the transmembrane potential of the oocytes in the presence and the absence of a substance suspected of being an inhibitor of KCNQ5;

(c) measuring membrane potassium currents following step (b);

where if the potassium membrane currents measured in step (c) are greater in the absence rather than in the presence of the substance, then the substance is an inhibitor of KCNQ5.

19. A method of identifying activators of KCNQ5 comprising:

(a) providing test cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) exposing the test cells to a substance that is suspected of being an activator of KCNQ5;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

(d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

wherein if the amount of FRET exhibited by the test cells is greater than the amount of FRET exhibited by the control cells, the substance is an activator of KCNQ5;

where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been exposed to the substance.

20. A method of identifying inhibitors of KCNQ5 comprising:

(a) providing test cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) exposing the test cells to a substance that is suspected of being an inhibitor of KCNQ5;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

(d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

wherein if the amount of FRET exhibited by the test cells is less than the amount of FRET exhibited by the control cells, the substance is an inhibitor of KCNQ5;

where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been exposed to the substance.

21. A method of treating Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, age-related macular degeneration, other forms of macular degeneration, deafness, epilepsy, different forms of neuropsychiatric, heart, gastrointestinal, and muscle disorders by administering to a patient a therapeutically effective amount of a substance that is an activator or an inhibitor of a voltage-gated potassium channel containing the KCNQ5 protein.

FIGURE 1A

KCN6q gene: DNA sequence

1. Underlined nucleotides in capitals represent exons.
2. Initiating ATG codon in exon 1 and terminating TAA codon in exon 14 are shown in bold italics
3. D6D280 genetic marker and phosphoglycerate mutase pseudogene are bold underlined
4. The exact lengths of the gaps between exons 1 and 2, 2 and 3, 10 and 11, 11 and 12, 12 and 13, 13 and 14 are unknown; these gaps are presented as runs of ten **bold n** as a convenience only

```
   1 CTGGAGTGAG GCGCGGGAAG ATGCCTGGTC CTTGCCTCGC GGACTTGGCA
  51 GCCGCGTCCT GCGGGTCTGT CCACTGAACT GCTGAGGACT GCGGCGGTGG
 101 CCTGAGGGAG AGCCGCCGGG GCAAGCAGGG GGCCCGG***ATG*** AGCCTGCTGG   Exon 1
 151 GGAAGCCGCT CTCTTACACG AGTAGCCAGA GCTGCCGGCG CAACGTCAAG
 201 TACCGGCGGG TGCAGAACTA CCTGTACAAC GTGCTGGAGA GACCCCGCGG
 251 CTGGGCGTTC ATCTACCACG CTTTCGT**nnn nnnnnnn**ttc cttttctatt
 301 cttattatta atatatgatc ttattattaa taatataaag gaatagcaaa
 351 tgagaatcca tgagcaatat cagaccatga aaatgagcca gtggctgagt
 401 aacaaccaat taggacactt gatagtttag caaagttgcc aaacaggaga
 451 cagactcggc tcctttgaac gaagagtgac tgcagtgtgg attccccaga
 501 taggagagca agaacatact ttctgggcct ctctcaggat cgttgtttgg
 551 gaaggaagtt gtatgggaaa ttcacaaact cttagatgct aacatttaaa
 601 tgcagcatgc cacacacaca aacccacaaa cacaaccttt ttttcatcaa
 651 taaaattgca gaggagcccc atttgcacag tatatcacat tgtattttaa
 701 tatccaaaat ggctagtccc ttccagagtt tttatgagtt aatgtgtgct
 751 aatttaatgg gcctggtgct ttattcattt gaagcaagaa attaagtctg
 801 tgataataag gtaaggttct tatcagattt ctctttttgt tgttttacag
 851 TTTTCTCCTT GTCTTTGGTT GCTTGATTTT GTCAGTGTTT TCTACCATCC   Exon 2
 901 CTGAGCACAC AAAATTGGCC TCAAGTTGCC TCTTGATCCT Ggtaagtgaa
 951 acatgaacaa gaacgtacat gaatgttgta taagaactgc ctataacatt
1001 tatactatgc atcttatcct acaaaaaaat cctatctaaa aaagagttac
1051 tgagaaatat aaaaatgtca aagattactg aaacatttgc ccaccaattt
1101 aacatgtagt caatccttag aaatatatag aaatgttcag gattgctatt
1151 acacagcaat atcttgtgtt gtagatatat cataaataga aggcaatatt
1201 agaaagcagt tttaagtatg tttatctatg ctaataaaca aattatataa
1251 gaagaatcag tatctatgag gcctctcatt atattgtgaa agactataga
1301 gtagagagca ttttccaata actgtaattt ggcagtagct aaatataatt
1351 ggccaagaac tatgaacata tggcacctca taagaaaata gaaggctcct
1401 tcatgctctt ttcaaccaac agactgcatt atgagttttg ctgctaatgc
1451 agttacctgg tgataaattc tgcagtttgc tctgtttcca ttatgctgtc
1501 aatcctcaac cacacagaat tgctcaattc actttnnnnn nnnnnacgag
1551 gtcaggaggt cgagaccatc ctgcctaaca cggtgaaacc ccgcctctac
1601 taaaaataca aaaaattagc tgggcgtagc tactcaggag gctgaggcag
1651 gagaatggcg tgaacctggg aggcggagct tgcagtgagc cgagattgcg
1701 tcactgcact ccagcgacag agccagactc cgtctcaaaa aaaaaaaaaa
1751 aaaaaaaaaa gagtatactt gatttatggc atgagtggtc ttgaatgatt
1801 ttgatggatg actggaaaca attagagata taaataaata gcacagaatc
1851 atgacagatt tcatgaagaa tacactgtga agattcacat ggttaataac
1901 attgaaatta ttaaaataaa agagactgca tatattagat ttttctttgt
1951 gatctagttg ttcaaagcag cagaaaactt taaattttcc ttaattttga
2001 aagtgtgatt aatggaatat tgttacaatg ccattgattt atatactttg
2051 aggatagtta acttctttat gtttattaga aattgcactg agagctaata
2101 tgcagtttct attggtggtg atatgttctg ttaacagggc ctcctgtcag
2151 tttttattct gagatttctg cctttcctgt tcttttgcat gagcctaact
2201 gactgagttt caatatcaag ttctgaaagc aagtgagcat actagtgtgc
2251 atgcaatgtg cacagaaaga tgtgttttcc tacctctcaa agctcaccaa
2301 aggatattac tcatattgcc acaaagtaca tttacaccaa taacacatac
2351 tttggtaatg ggaaaaataa ataatcttag gtaataaaat gcactttggt
2401 gcttataaag gaaaataatc atcacaggta gaagaggagg aaggcaagac
```

FIGURE 1B

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2451  taggttttga ttcaaaatgt tttctgtttt gctaggaagt ctagaaggaa
2501  tttggtcaaa tgacctgagg aggcaaggag atttctccca gtggcacatg
2551  gcagtccaca agaagactag gggcagggaa acaaagcaag attgtatctg
2601  atttctacag gactccaaca ctaccctgcc aatacccttt tctcctctga
2651  aagccatgat cccaaaggtt tccatttctt ccgggttttt cacattctac
2701  caacaagcag aatgtcttcc ccactgacag ctcaacagtt gagtttttcg
2751  gggttctacc ccttcatcaa cacagccttt gctttcctgg ttactgagta
2801  aataaaacac actggccact tctgcttagc cttcaggagc cactctggct
2851  ccaccctgaa gttccatttc ctccaagaac taagacattt ggagattctg
2901  cctaaaatat gcttaaataa aagggataaa ctgtctctca ctttctttcc
2951  cccacagctt gtcttaagaa caacggtgta accattagtg aaaaatcctt
3001  tcaggctagt aaaatgtaaa aagagaagag gtatcgggta acaacaaatg
3051  aaaataaaat cattcagtgg tagaaaccat aggagtgaaa ttaggtagtt
3101  actgtcctcc agcttacatt aatcaaaata agcccacact gtcactaaga
3151  catcttgcag taagaagcca ttcaccctct cattgcaatt agtgtcataa
3201  agctgaatag acaggtcaga aatgaaaatc ataggccaat taagttattc
3251  tcatttttcc acctccagct agctcttttt gagaattttg attttaatag
3301  ataataaaac agtatgctaa ttgggtggtg ctgagcctga agccgtgaac
3351  tgaaggaaac ttcaacaaac atttggctag ggcctgctct aagcagaggg
3401  gctacgacaa tgggtaaggc atttctctag aaaccagcac tcagcagaat
3451  ttctggcacg agattttgtg agttttctag tggtgtgtct tatcttcccc
3501  caatagatta taaactcctc gagggtgaca gaacacattg ctgatcttta
3551  tatcctgcat gtttatggta ttcggtagac atttataaaa tgaattcatg
3601  aaaagcagaa catctagaaa tgaagtcaac attgcagaga agttagctat
3651  atgaaactct gtaaatacce tcaaggaaga aggaagaagc agattttctg
3701  gaaatcaagg gacctcccag tataagagca attcctttgg tccaaagaag
3751  ggcagctata agaacagaga cataactcct ccgtaagaaa agataaaaat
3801  tctgaaagtt ctctaagaac atgcccagcc ctgacctgcc tctcactctc
3851  agtagcatgg aagccgtact atctcttatc ttgacacaag catccacttc
3901  aatccacagg acaaatatca ccaatatgag aagataagat ctgttttata
3951  gtcaacttgg ctgacatgta ctaatttctc aaggtcagga tagctctcta
4001  aatagaaata cttgtttgtt ttaaggaatt ttatttaaat ttgtgtatct
4051  taaattttaa ttttgatctc ggctcactgc aacctccacc tcccaggttc
4101  aagcaattct cctgcctcag cctcctgagt agctgggatt acaggcacct
4151  gtcaccatgc ctggccaatt tttgtatttt tagtagagac cggatttcac
4201  catgttaacc aggctggtct caaactcctg acctcaagtg atctgcttac
4251  caaggtctcc cagagtgctg agattacggg catgaaccac tgctcccagc
4301  ctcatgtagt tcttaagagg aagaaaagcc tatagattag tgagaagtag
4351  acaaattagc aatttgaatc aaatgaaaac ttggtttgat ttcattcatt
4401  ttggagacac tttcggtgtt tccattttga tctgattcag gacactgatc
4451  ttcgattcta agttgcactg gttaatttgt gattatttta caaaatcata
4501  acagaataca tatctgggtc cagttcaagg tacagcaagc cattttcaat
4551  gtttccagct tggtgtttat gattcataca tgaatcattt gggcatgcag
4601  acacacccaa atagaaacct caaaccaatt aaggtataaa taggtttagg
4651  atgggggagg atggacaaca aaaaaaacct cagtaaggct cctccacaaa
4701  gggcaccact tcagcttggt cccatgggca gacttcacct gtggcaggtg
4751  aaggggaaag cctaagacat cctgtgccct gatgcagatg tgacttacag
4801  aacataaaac gtaaaggcag aagggatcat ctgggtggct gctcatacta
4851  ggcaggcatt atagctgctg acaagagcca acccatccct aaggatctaa
4901  aatcactaca agagaggacg gaagtcctct catcatggca tcccaactag
4951  taactgggat gcatagggcc actccaggta ggcagcgagg ggtaaaccag
5001  gaatgtcctg ctgttcccac ctcttttccc caagcagggg gcacccactt
5051  cctgcctcca gcccatatgg tctcaattta tggcctcaat acctgataaa
5101  aaaccagccg tgatccttcc ttagtaacaa agtgtcaatc agtcatttgg
5151  aatggggcat tttcaaacta ttgcctccct atgatcttct gaagaacctc
5201  tgggataaat gaacattgtt atttaggtat ggttaaatga attacttttc
5251  aggagcagat ttatatatta acaggtgtga aaaacttgaa tggataaatc
5301  atttataaag aaatttcagg aatcaactaa tcccaagggg aaagacccac
5351  taagacacta gattttgctg gagctactca aacaaattca tctatcatat
5401  ctacctaagc cttccaatca atgagactag ccgcagtgac actgtctgtc
5451  aaaactacct cagtcatttt tttccaaggc aggaagcatc catacccctt
5501  cacaccttaa tctaatttcc cctatctcca ccccactccc acttctatga
5551  ccccccttccc cccataccca cccccgaagc atctactagc caacttagtg
```

FIGURE 1C

```
5601  aagttctgtc acgctctcac aaccacctct gtgcagcaat gattctgtaa
5651  atatccatgt gtcctcaaca ccaggtcaaa ttagtccctt tggtaaaaac
5701  attcattccc tcaaattctc ttccaataca ctaatatacc ttcccaaaaa
5751  gtaaggagaa gcttgaaagc tagctggatt gatgatggta tgtgatgttc
5801  tataagttat agttagtaag catgttttta ggatattttt ctgctctcca
5851  aagagacaca attccggaag atatttactt ttgtgtattt ccacattttg
5901  gtttaagttt ggagccatct ctagatctta atttcattcc cctaatatgt
5951  gttatactag tagaattttc caaattacat agaattataa ctgcaactct
6001  tctgactgat gccttttttt tgcattttat gatgcagttt acatcacaaa
6051  ttctttccct gcagggatta tgtaaagagg catgttgacc tgctagccct
6101  atgttacttt aagtatatgc acacacacaa aaaggaacaa aaacagctgg
6151  gaattgatta tgttgatatt ctgaataaaa gcaatagttc taattatgta
6201  tgtctaatta gccacagctc ttcaagaatt gctgcaaatg tcacagggtt
6251  tataatgtcg gcatttcatc ttcacgaaaa tgctatttga tggcataaaa
6301  ccagaaaaaa ctaatggtca cagaagacag cttgtagatt agacaaaggt
6351  cactgtgttt taatgaacag tgctgttaat taatgagaaa acaactggta
6401  catgagcttt taagcattgt gaatttgtac ccaaaaaatc aatctgccta
6451  aaacaatttt aagtagctaa aaaacaaaat aacggcaaga acataattta
6501  aacctcaaat ggtacagcag agttatatgt atcaattaaa ttgaatcaca
6551  gttctcaggt gtgacatatg aagaggcttc tttaatgcct ggaaaagagg
6601  gttaatatgg attggtattc tcaatacata ttgtagataa aattcaagac
6651  tagctctacc actgcctctt ttctttttct ttttttttct ttatttgaga
6701  cagtatctcg ctctgttgcc caagctggag tgcagtggca tgatctcggc
6751  tcactgcaag ctccgcctcc cgggttcacg ccattctcct gcctcagcct
6801  cctgagtagc tgggactaca ggcgcccgcc accacaccca gctaattttt
6851  tgtattttta gtagagacgg ggtttcacct tattagccag gatggtctcg
6901  atctcctgac ctcgtgaccc acccgcctcg gcttccgaaa gcgctgggat
6951  tacaggtgtg aaccaccgcg cccggccacc actgcctctt aggcttctta
7001  atttccttat catttaagaa gaataagaaa atgcttctat gttttaccaa
7051  aattctgtga ggacaaatga ggaaccattg taactcctac aaggtgagtg
7101  ataaaaataa tacacattta ttgtctttgc ttttgtaaag agttatccaa
7151  gccaagcttc taggggctta aataaggaag gacaggacca ttgttaataa
7201  catcaagttt ccactacagc tttcctccaa acaagtcaaa tattctgaat
7251  attattcact aatctcttta gctgccattt cagtaaatag cgagcatttt
7301  atttcaacta aaaccaagca agagaaaatg aactgcttta tcctgaggta
7351  cagcagcaaa ggcaccagaa cttgtctcat ggcttaccca gcaagggtca
7401  gaagaaccat ccctaattta aatcatctcg actgaatgta acagattttt
7451  gtattttcaa ctcatatgaa aataaaacaa tgagacctca tccaaagggt
7501  gatttagaga gtacctctaa acaaaacaca gtgaaaatag acccagcatc
7551  tggatttgaa gaacacattt cctcttacga gtctatccca ttgtctagat
7601  tgctggcaat ggctttttta aatttaaatt gttattgaga taattgtaga
7651  ttcacatgca gttgtaagat atagtagaca taccctgtgt atactttacc
7701  caatttccgc aaaaggtaac attttgtaaa actatagtat aatatcacaa
7751  ccaggataat aatattgata cagctcacaa atctcattca gatttctcca
7801  gttttacttg aatacatttg tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg
7851  tgtgtattgg ctctgtacag ttttatcact tgcagagatt agtatatcta
7901  aaacaacaat caagatattg gacagttccg gccgggcacg gtggctcact
7951  cctgtaatcc cagcactttg ggaggccgag gcaggcagat cacgaggtca
8001  ggagatcaag accatcctgg ctaacacggt gaaaccacgt ctctactaaa
8051  aatgcaaaaa attagctggg cgtggtggtg ggcgcctgta gtcccagcta
8101  ctcgggaggc tgaggcaggc gaatggcatt aaccagggag gtggagcttg
8151  cagtgagccg agatcgcacc actgcactcc attctgggca acagcgcgag
8201  actctgtctc aaaaaaaaaa aaaaaaaaaa gatatcggac agttccattg
8251  tcacaaggat ctctcaagtt acccccttgct aaccacatcc accttctcct
8301  tcacacttgc acacccccttc ccttctccag cctgacccca gcagccacta
8351  atctgttctc catttctgaa atgtttttat ttcaaaaatg ttatataaat
8401  ggaataatac agtgtataac tttttaagac tgacttttct tgcactcaat
8451  ataattccct ggcaattcat ttatgttact ctgtgtatca atagttcatt
8501  catttttatt attgagtagc attccatggt atggaggcac cagagcttgt
8551  ttaaccatcc tcatggtgaa ggacatctgg gctgtttttg gggtctggtc
8601  attatgaata cttcttctgt gaacattcat gtacaggttt ttgtacaaac
8651  ataagttttc atgtctctga cacgaatgcc caagagtaca attgctgagt
8701  catatggtaa ctatatgtcc agttttataa gaaacgacca tgctcagaag
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D6S280

FIGURE 1D

```
 8751  gaccatactg ttttacattc ccatcagcag tgtttgaatg atccagcttc
 8801  tccgcatcct ccccagcatt ttgtgttgtc actatttttt gccactattt
 8851  tttatttttag tcattctgct agctgtgtag tgataccatt gcgatctaat
 8901  ttgcattttt ctgatggcta atgatgtcaa ataacttttc atgtgcttct
 8951  ttgccatatg tgtaacttct tttatgtatg tcctctttta tgaatatcct
 9001  atttatacct ttgccaattt tctaattgag tttttggttt tttactgttg
 9051  agttttaagg tttctttaca tattttagat attagtcctt tgtcagatat
 9101  gtggtttaca aacatttttct cccagtctat ggcttgtctt ttcatcctta
 9151  gtacctgggc tctcacagag taagttttta cttttgatgg agtccaattt
 9201  ctcatttttt ccttttataa cttctgcttt tgatgtcaag attaagaact
 9251  ctttgcttag tccaaatccc aaaaatatct ccatttttttt cctaaaagtt
 9301  ttattatttt atgtttaatt tttaaacccg tggtccattt ttaaatgatt
 9351  atcataagat aggaagtata gattaaggtc cacttttttg cctatagatg
 9401  tccaattttt ccagcatcat ttgttgaggg cccttcttcc tccattgaaa
 9451  tgcttttgca cctttaaaac aaatcaattg agcatatttg tgtgggtcta
 9501  gttctgaatt ctctattctg ttcactgttc tatatgtctg tatgttccat
 9551  atgtctatcc ctccaccaat ccacagtctt gattactgga gctataatag
 9601  taggctttaa tatcaggtaa agtgattgat ctcgttttat tcttctttgt
 9651  cagcattgtt ttagctattc caggtcctgt gcatttccat ataaatttta
 9701  aaataagttt gtatctaccc cccaaaaaaa actttgctga gattttgaca
 9751  ggaattttat tagacctgta gatcaatttg ggaagaattg acatctttgc
 9801  tatgatcagt cttccaattc ataaacacgg tatttctcct cacttattta
 9851  ggtcttttct gatttctttt atctgcattt cataatctca atgcacataa
 9901  accgtatgtg tttttctaag tggatattta agttattttt atttggaatt
 9951  attataaata ataattttgt gtttctaatt ttcatttcca catgatcatt
10001  gttagtataa agaaatatga ttaattttta tattgatcat acatcgtgca
10051  gccttagtga actcacttgt ttcaagagtg tcttcgtaga tttcttggga
10101  tttttctgta gaccatcatg ccatttgtaa atagagacca ttttatgttt
10151  acctttccaa actgcatggt ttttttttctt ttatttggct tattgcagca
10201  actattaata taacttacaa tactatgttg aataagagtg atgaaagtat
10251  acatcttggt tgttcttaat gttggggaaa agcattcagt ctttcactat
10301  taagtatgat gttaagtttg ttgtaaatgc tatttatcga attaaactgt
10351  taaacctctt ttcctaactt gccaagagtt ttttttaatc ataaatgggt
10401  gttggatttt gtcaaatgct atttcgtcat caatttatgt gatttttttt
10451  tagctttatt atataatgca ttatattgat tgatttcaac cattgagcta
10501  gccttgcata cctggaataa atcctacttg cctatatatt gactgattga
10551  ctgtttgcta atattttgct gaggattttt tgtgtctaag tttatgataa
10601  atatgggtat gtagtttttg ttttgctttg ttttattgtc tttgtctggt
10651  tttggtgtca ggataatact gacttcataa aatcattgag aaagtttttt
10701  ctcctctatt ttctgggaga aattgtgtga aaatgatata ttcttattta
10751  aatgtctggt tgattttgcc agtgaaacca tttgacctgg acatttctgt
10801  ttggggagat tttaaactat gagttcaatt gctttagcgg ttatagggct
10851  acctagattg tctatttctt ctttgttgag ttttggtagc ttgtagtttt
10901  aaaggatttg gtccatttct tctaagttat caagtgtatg tgcgtaaagt
10951  taccatagta ctccttcatt ttttcagtgg cgtagaatct atactgatat
11001  cccctattac attcctgaca ttggggattt tcatcagctt tcaagaaaga
11051  gatttatcaa ctttattgat tttctcaagg aaccactttt ttgtttcatg
11101  gattttccat attgttttcc tcttttcagt ttcattaatt tttgctcttt
11151  tctatgttat ttccttctat ctgcttcctt tgggtttatt ttacccttct
11201  ttttccaatt tcttgaggta ggtactcaga ttattaatat gagaactttc
11251  ttcatctaca atgtaagcat ttagtgctat aaattttcct ctcagcactg
11301  cttttactgc atcctacata ttttgttatg tcatttttttt attttcattc
11351  agttcaattt ttttaaaatt tttgagactt tctctttgac caatggacta
11401  ctgggaatat tgtttaattt ccacatgttt agagatttgc ttgttgtctt
11451  tctgttattg atttctagtt ttattccatt gtggcttgag aacacattct
11501  gtctgatttt attcttttaa acttgttgaa atttgtttat gacccggaat
11551  ataatctatc ttaataaatg tgcatgggtg ctttttaaaa atgtgtattc
11601  tgctgatgtt gggtgaaatg tctcatatca gtcagatcct gcaggttgaa
11651  tgtgttgttc aaatagttca catacttgtt aattttcatt ctagtagtgc
11701  tatgcccata gttctgagca aggataaggt gggttgatga agttcccaaa
11751  tacgacttaa catttgtcta tttttccttt cagccctatt ggttttgctt
11801  tatgaatttt gagactgtct tgtcattttc ccctcacctt cttaaaaaaa
11851  aaagcagcaa gcaatatttc tgaacaatag ggcttgaata aagaacttgt
```

FIGURE 1E

```
11901  aaatgtactt tatcctgcct tactgcagca gaggaatagt gcagtgacct
11951  tggcatacct aagaacaatg ggcatatatc tgtcatttgt taagaacaat
12001  ggacatattg gtgtcatctg tttccatgaa aaagaaaaat tactacacag
12051  tagtgttcgg gggctcaggc cacatttggg attttcttgg gatcccttat
12101  aatatgagta ctcacaactg gagtgccaaa tgtcctggca taagcaggaa
12151  ttaggggcag ggattaaaaa gtggatctgc cattcaacct aggttgggca
12201  caggcacaac tacatgggca ttttgggcct gagtatgttt tccatatttg
12251  gaaagatgtg ctggattaac aagaaatgat ctggcacttt agatacctta
12301  ataaatgaac agactcaact acccagatat acattcaaaa ccaaaacaaa
12351  gccaaaatca aacaaaacct tcggattatt aatgaatgta tgttgaccct
12401  aattttggtt atctgtgcat aaagtcatct ttgaaggttt atcctataag
12451  taattttgaa taactgtgag taagcagtga tgatattggg tatttatttc
12501  ccatcatgag aaatatttgt ggattactta gtgcaaaata agagaaggat
12551  agaatgatat agctctacta ggcatttcaa aagtgcagca tatcatcaca
12601  tgctctaatt aaagaaacag acatttgcct gaaatttgca acaaaaatgc
12651  cacttttata aatttggtaa cagtttttat cctgcgagta agaatgggag
12701  aatggggagt aggttagaat gtttactttc tctgctttgt atttctgtga
12751  tgtttggaag ttttaataaa gacaatatat tacttttaca attaagctat
12801  tataacaaca atctataaat attgttctac attataaatc ttgaatcaac
12851  cctcgtttta aaacaagaaa gtgaattatt ttttaaagga aaaacaattt
12901  tgataaataa agtgcctgtc cctatagaga cagcaaggtg actgtgctaa
12951  gcttgctcca gaaatgcttt cgttttacaa attccatttg gtttttcatt
13001  ctatcatcga ctgtttaatg agccactcta gctggccttt ccccagggtt
13051  aactcacaac tcttcctaaa taatctcagt cattttcctg gagcaggtgt
13101  tgttttctag gcagctcttg ccaaagggca gcataataat taacaagctt
13151  cagatctgga ggattcaggg tctcatttct ggcaaaggat atgtgtgtca
13201  cactgtaatg cttttgaaac ttactgtttt ataaggagat tttgacactg
13251  taacgaaaga attcagtata cttcgaaata tttgcttctt tttctctaag
13301  aacaactctc gaagatttag agattatgtc actccttgca gcaaaatgaa
13351  gctctatttt ctgtaaaact tgccattata tttcaggatc gctattttat
13401  ttcagatatt tcacatgtta ctgggtagct aaagtcagct acactataaa
13451  ttccagacga gacagatcca ttattcagcc tgcacattta gtattgaaac
13501  tgactcccaa atttacgaag cattaatgac ttgaaaagga atagcattcc
13551  atgataggaa atgcagacag tatgaggttc aaatgctgtc cagatttagt
13601  ttgatctgga gaaaggaaat gttcttaact ttagatatta acaactagat
13651  cctttagaca aagtgcctaa atgtccaaaa atatgcatag agcttcttac
13701  tgtggtttgc tccataatgc ttctctctga tatgtcttat ctgatatttt
13751  agGAGTTCGT GATGATTGTC GTCTTTGGTT TGGAGTTCAT CATTCGAATC
13801  TGGTCTGCGG GTTGCTGTTG TCGATATAGA GGATGGCAAG GAAGACTGAG
13851  GTTTGCTCGA AAGCCCTTCT GTGTTATAGg tgaatatcag agtctcagat
13901  acctggacta tgacaccaac attcttgtct tctatctcct gttttgcaat
13951  atttgattaa tattaaaagc taacatccat ggagtactta tcatggaccg
14001  ggcactcttg tgtcttgaaa atgttgactc atttgatgtt gtctccacag
14051  cattatgagg tagatatttt tattatcccc attttacagt tgaagaattt
14101  gagacaaaga gagacggagt tagttgctga atgtcataca gctactaagt
14151  ggtagagctt gaattttagc caggcaatct ggctctagaa tacccactta
14201  tatcaattaa cttatatgga aatacatgtt tctccagtgt tgccctaatt
14251  taggggaaca ttgatttcag tgagtataaa aaacccttt tgctctacaa
14301  tatgacacca gtttatgctc tggatcagct ggaatagata gccatacatt
14351  ggtactggta atgcatatca attaacattc ttcaagaatg attataagta
14401  tggtttgctt aatgcattgg taactgtaga ctggacaaag tgctctacac
14451  tctgaaatat gaatccccca ccctccaatc caaaatacc aaatacatag
14501  cacatctctg cacctcccta gctgccattg tttctgagag acatcattca
14551  cctgggttct agcttgaaat tgtacttcct aatgaagatg ccatagagca
14601  ttctggaatt aagatctagc atttcccagt aatatttaaa agtattataa
14651  aatggaaaag tctatatata aaagctatta ttattattat ttagtagcta
14701  aatttggctc tcttgctttt ttgtctttct cacttcctag gcagccattc
14751  aaatccaaat actgaaaatt cttgatgagg cttatttatt tcaactattt
14801  tcaacctgaa aaagtaggtt tttaatttac aaaatagttt aggctatctt
14851  ctacagctac cacaggtttt ctgttttgtt ttaggagtca ggaattgttg
14901  cgtaatcttc tcagtttcct cccttactcc tgttccctat ggtgggggca
14951  gagtggattt aaggaagaaa gtgtatcacc atccatgggc actgttaaga
15001  agaatccttt attccatact tctttcatag tatgcacatc tcaaaagtct
```

Exon 3(D)

FIGURE 1F

```
15051  ccacttatta aaccagaatt tatggaaatg tggctgtgtg tgaggcactg
15101  gtgttacaat agtgaatcta gtggaattct cagttaaatc tatcttaaaa
15151  taccttgttt ggccctcacg aatgcagtct gtttgtctgt cttctccaat
15201  aataggcttt actgcttttt ggaagccatc atgctaaggt atggagcaaa
15251  gtcggtggta actccaagcc ttgcaggttc ataaagcccc aaggcatatt
15301  agtgaaggca ttagattttt ctccctggag atgcttttt ctctctgaat
15351  tctctactca ggcagcatta caaaggactg taacctgatg tgaaactact
15401  gcacaacaag tactttctgt cccataaggg gcccaaacaa aacaattcac
15451  aaggcagatg gttagccaag attcactcaa cttctacagg ataaggtcag
15501  ttcatggatg actggaaaaa tgtttcattc cagattttaa aaccaattaa
15551  aaattggttt tgttccaatt tcagaagcaa tgccaatgta tctctggcct
15601  ccatgcgaaa aagaaagctt tttcccagat gtctgctgcc ttttgatagc
15651  tgttttcagc tacggataca tcaacacatc ttagtccttt agtctttctc
15701  ttcctgcctc agatccttgc aggtcttgat ataatatgta gttctaaaaa
15751  tgatgttatg ttatctataa tcttacttgc ctttggatgt atcaatagtg
15801  accttaaaaa tttagtatga tgcctggcgc agtcactcct gcctgtaatc
15851  ccagcccttt ggaaggctga ggaaggcaga tcacttgagc ccaggagttt
15901  aagaccagcc tgggatggaa agacctgtct ctacaaaaat ttaaaaatta
15951  gctgggcatg gtggcataca cctgtagtcc cagctactca gaaggctgag
16001  actggaggat catttgagcc caggagtttg aggctgcagt gagccatgtt
16051  cctgccacta cactccagcc tgagtaaaaa gagtaagacc ctgtctcaaa
16101  aaaatactag tatgacatgg tttacgcata attgcagttt tgttaaccct
16151  tcagaccttt tctttattta gatattttac ctctaggaaa ttaattgctt
16201  tggaagaaaa tttcatggat aaatatataa tgaatcccca ttagaacaaa
16251  gtctagattt gtacttacag ttaggataat tatgaatttt ttagtctttt
16301  attaaatgta catgtttgac ccatggtcca gctgaatgga tgttatagtg
16351  aagcatgttc aaatgtggct tatcagtatg aggtcagtaa aatttaacct
16401  acacaaagga atcaaacatc accttcctga aggcagcaag ctgtaccaga
16451  tgactgttga gactatttct aggcccgttc aacaggttca taaaaacgct
16501  tgatgtaact ggtaaaatac taaagtgaac actgtagtcg ccttgttcaa
16551  cctaatttac tgtgacaaaa tgaaaaaaga aatagcatct cttatctgtc
16601  cctgataact gttctgaatg ggtgtttgga aatatagcta aaacctccca
16651  aaacttcatg tatttgtaag atttgattac tctgaacatt ccaagtacac
16701  acccaaatat ttttagaagt gttgagcatt cgagaaaaga acatagaaaa
16751  gattgtggta gactggctgt gccttcaacc tgggaaatgc tttctgtaag
16801  cacaccaatg tttttctttc cagttggaaa tacactgaag ctgctagagt
16851  ggtcagctaa caagccccat gtactattgc accctattga caaaggccca
16901  attgatagag gttttatggg ctaattactg aaggttttag catgtccctt
16951  tctgaactgc ccaccttcct taccctgca ctctagccaa aaccaagagc
17001  atttcaaaag cccactgatc tcacaaatcc taaaatcatt acatatttgt
17051  gtttggaaaa catattttaa acaattataa cataagggaa gaaataaatc
17101  tatttaactt tttttaatta ggtactttgt ttcattacta ctgtacattg
17151  atgtatgtct gcttggtttt aagcatttgc tttgaaaatt agtaaaatct
17201  tatctagaac ataaaattct tcctcatatc tatgtgttca atttttatct
17251  ctcccctaag actcttctgt cataataaca ttctatagct atgagcacta
17301  attgctgtat tgctgatgtg gatagtcaag tgtgttttgg gatgaccacc
17351  caagctgccc ttcatttacc cagactggct gctttatgat ttctctatgt
17401  gaaaacacaa aacactcacc caataacatc ggcataaaga atttgtgaat
17451  aacctctaag actgatttca tagtcattct tttttctagc tttcattact
17501  gacctaccca aaaattgcaa atagacctaa ggctgaaact tggatcacaa
17551  taatgagcct gatgtgtcag gaagccaaca aattacttct cacagtggct
17601  ttttttagat tccttggtga cgctttccaa aggcagatat aacagggcca
17651  tatttttcag tcttgcaggg agtctcagtg agaaaatacc agcctgttgt
17701  tagtcttgga tctgcatttg atgctaagtg taagttgatt tcttattgtt
17751  attttaacag tttattttca gtgtaattat ttccacaaga ggacaaaaga
17801  ggaataaaat aaaattttat tttatcctac gtggataaaa taaaattgaa
17851  gcctttatta aaatcgacca catggctgag actactctaa tatatctatg
17901  atttcatctt attaaaaggc aacttaagtt gctaatgtgt tcaaaagtta
17951  gatcagactc ccaaaactgc cactgtgttc taaattgatt ttgagacatc
18001  atttttctgt ttctctgtct tctctatctt ttgttctaag agacttactc
18051  ttcaatggca ttatttttcta taccttctac tccctttttcc ctttagtaga
18101  aattatatta tttcacttat tttctgttag tcatacactc ttctgcaact
18151  tattacttct aagtgttcaa actccctcag tgcatgtaga ttccttccat
```

FIGURE 1G

```
18201  gtgattaact ggaccatctg aggacaatta aaacctgttg gattggctga
18251  tcacaaaaca ttaaaacaat tttaatccct ctagttagta atagctgata
18301  tttattgaga actactatat attaggtact actttaagca ctttataaat
18351  atggtcttat ttaattctac ataagtacta taatgtcctt atttatttta
18401  ttttatttta ctttacttta ttttattcta ttttatttta ttttatttta
18451  ttttatttta ttttatttta ttttatttta ttttttgagg cagagtttcc
18501  ctctatcacc caggctggag tccaaatggc atagtctcag ctcactacaa
18551  cctccgcctc ctgggttcaa gccattctca tgcctcagcc tcccgagtag
18601  ctgggactac aggcacacgc caccacaccc agctaatttt tgcatttta
18651  gtagagatag gatttcaccg tgttggccag gctggtcttg aactcctggc
18701  ctcaagtaat ccacccgcct cagcgtccca aagtgctggt attacaagtg
18751  tgagccacca cgcctggcct ttataatgtc ccattttata gatgaggaag
18801  taagacaaga ctgaagactt tatagatgag gaagcaagac aaacttaaaa
18851  agatgatagg tgaaagaacc tggatttatt tctcatgatt tcactctaga
18901  aaaatataca tacccaactg gaaaattgtc tttactgttt attagcattt
18951  taaaattaaa tttaattgaa ccttatctat tgtcatcaac ttgtaaacag
19001  aagaacatga tactattatg cttatcatta gtaattcaag atctttaaag
19051  aaaagccagg ctttatagaa cattaattgc agtatcagcc ttaattatat
19101  caactaaatt atgttaccta ttgctgctct ctaacctgaa tgggaaatta
19151  ggacctaaaa tagacttact tacctgtatc aaacttgcat atactcttca
19201  gttgttgtta tcatgaggct ccctgtgtat ttccaaattg gagacctctg
19251  gagagcaagt aacattactc gcaggactac cttcaaatgt tttttaacat
19301  taataaacta tcggtaattt agataattgt tgacctggta cacaaacttg
19351  aaagttgaac ttacaagaca gcttgattag ctgatatggt tggaccacat
19401  gaagaaaatt tatttccgaa gaggaaaatg aataaggatt atttcccact
19451  ctttctataa actttagtag agcactatga tatactgtat taacattctg
19501  tactatcaca tgttacataa gaaaattcat tcacagacag ggtatttatt
19551  atgtgtcaaa cataatctta agtataaagg atacaaaagc gactaaaaca
19601  cggtccctgc ctgtaagaat agaatctcct gtgcccttag agaatggcaa
19651  aacttaaagg aggtatacta taattatggt gttacagagc aaaggtgatg
19701  gaaattgaag tagtcctaga aagaaggcta tggaatatca tgagtgattg
19751  tataaaacaa agaagcaaag gactaccccc aggttttcaa attatgtttg
19801  agtcatccac tgaacattta tacaatttct accatgtcca agcatgctta
19851  tggatgctgg agaggctgta tggcaccaaa tgggcaaggt cttccttctt
19901  atagagataa tattcgtgtg gacaaagaaa aacaatacac aaatatgttt
19951  ttgaaaaaca agataatgtc atctacagat aagcacaatg aagaaaataa
20001  aacagaaaga gtagaggcta ccttagcttg ggtggtctga gaaagtcttt
20051  ctaagtagtt gacacttgag ttgacctgaa tattaagaag aagccagcca
20101  tgaggaggtt tagacacaga tctttccagg ccagggaata gtaattgcaa
20151  ggattattaa cacttgatga gcttgggttg tacaaggtgg agacataagg
20201  tctcgtggct ggagctcaat gagcagtggg gagaatagca gaaggtgata
20251  ggggagacag gcagaggtca caccctgaag gccatgtagg ctctgctacc
20301  ctgaatcaag gttccttcta aagacaggcc accaggcaaa ggtcctacgg
20351  gttgctggca ggcctaatat gaatactatt caggttatga acagcagcat
20401  taatcaggca acaaaaagta tggctgttta atgccctggg ttttttagtc
20451  atgtatgcct gttggaactt catatcagca atatacaaat tattacccat
20501  ttatgtttat aaaaaacata aacataagtt tataaggaaa taatcctctg
20551  aattttgttt ctatatttct gcccttagaa acatgaaatt ttacattgtt
20601  ttttaaaatg ttatttttct atgaggaact ggaattagaa tgtgatggaa
20651  actttttttac agccccagtg gtatcaccag taagcagttc ctaagatcct
20701  ccttgccaag ggactctatt ccatactctt agttatgatg attgcagtgc
20751  agaattattt cattaaagat tgtttatttc ttttgagaaa ttgtcccttt
20801  ttgccttgag atgttatctg aaactgtatg atcaataaga agcattaaac
20851  tgtcactatg gggtaaattt tcaaagtggt gcctgcaatt tgccagtatg
20901  agtcccatta acttctgtgg aagtcctgca gttaaacccc tgcacatggc
20951  tttgaaaatg ttctacaagt ttgtctttgt ggtgcctttt ttatttttaa
21001  taaatatcac agagcaactc agtgcatagt tgattgcagt atttaagaac
21051  gtggataatg tactgtgcag gaggagactt ttaaaattag attttaaagc
21101  ttcatttcta ttaagagtca caacaacaat ataaatacat ctttagttct
21151  tcaaagagca cctttctata aaggaatttg gagctcaatt agaatataga
21201  gcttataaag cagcaccatg tccctctgag acattgttta cttcactcta
21251  tagatggaaa agtcgaggca ctgtgaagtg ggggtgcttt gtccttagcc
21301  cataaatcag cagtaaagct aggaatagca tgctggcctc ccaatagctc
```

FIGURE 1H

```
21351  attgctctaa agcactgcct cttgttagag tcaaatttaa ttatagtata
21401  atccgtttaa tctacatgtg gagaaataat gaaggagcag gaaaaatgaa
21451  tttcttaaca gatcagtgga aaaccatatt acatagatta gcaactgtct
21501  tttcaagatc cgtattttcg gcatgtacta gatggtatct gatgccatga
21551  aagcaaatat tctaattcca ctggccagaa ctggcaaaga acttcttatt
21601  ttcctcactt tgaaacataa gtaaaggggt tccacttgaa aattaataag
21651  ccatgtgata tgattcgatt cctgtcccca aatctccctc cttctagggg
21701  ccattgtcta aagtctaaaa gaaaacatac caggcacagt ggctcatgcc
21751  tgtaatccca gcactttaaa gggagagcaa ggtaggagga tcacttgagc
21801  ctaggagttc aaaatcatca acctgggcaa cataatgaga ccctatctct
21851  acaaaaaaaa caaacaaaaa caaaaacaaa caaaaaaaac tgtaatagct
21901  gggtgtggtg gaacacactg gtagtctcag ctactcagga ggctgatagg
21951  agaaggtaac ttctgcccag gaattcaagg ctgcagtgaa ttatgattgc
22001  accactgtac tgcagcctgg gcaacagagt aagacagaga gagagagaga
22051  caaagagaaa ggaaggaagg aaagaaggaa ggagggaagg aaggagggaa
22101  ggaaggaagg aaggaaggaa ggaaggaagg aaggaaggaa gggaagaagg
22151  aaggaaggga gggagggaag gagggaggga aagaaaggaa aggaaagaaa
22201  ataaatgtaa ctattataaa agatgttcaa tgttttattt tggaataact
22251  ttagacttac ttagaagttg caaaaatagt acagaatttc catgttcaaa
22301  tgtactcttt acctaacttt ccccaaaata ttttacctac gtatactgca
22351  attatcaaaa ccaggatatg aatacatact attagctata gtctttattt
22401  gaatttcacc agtttttaca tgcgctcaat ttttatatac actcctataa
22451  aattttctca catgtatata tgcatttaac caccaccaca atcaaaatac
22501  aaaacttttc catcacccta aataaacttg gaatgatata ctttgtatta
22551  ttcctttaca ggtactccct ctcttcaatc ctaacctctg ggaaccacta
22601  tatctgttct gtttcactgt aattttgtca tttttataat gttatataaa
22651  tgaaattgta aagtagtaat cttttgaaat tggctttttc ttacacagca
22701  tgatgctctt gagatccatc caagtgcatc aatagtgcat tcctgtttat
22751  tgcttaatag aattccatga tctagatgta acacaatttg tatattcatt
22801  tacctaatca aggtcatttg ggctgcttct agtttttggc tattacaaat
22851  aaggcagcta tgtacattca tgtgtaggtt tgtgtatgaa cgtaagtttt
22901  tatttctcta gggtcatata gtgctagttc acctttatca gaaactgcca
22951  aactatttcc ttttaaaata tagaaatgcc aatgcaaaca tgtgcatgga
23001  ggtcagcagc cccacccccc gccccacgct gccactgctg ccagtgtgaa
23051  catatgcatg gaggctggca gccccacgct caccactagc ctgcccctgc
23101  actgacactg ctaccagcat gagcgtgcac atggaggccg gcagccccat
23151  ggccaccagc actctgcccc agttgatgag cattcacccc accacactgc
23201  cacttgctct tggcactgct cttggcactt acaaatgagc acagatcctg
23251  ctgccaccac cccaacaaag tggtttggct ggcaccaccc atcagagtat
23301  tgtggccaga ggtgcaggaa caccttagcg cctccacttt agcagtttcc
23351  taacctcaag gggccagaga ataaagtcag agatccagta acagcctccc
23401  aaagttgcag catacagccc aaaagttctg agctgagcct tacccctaa
23451  attcttccag aaatgaagcc agtcaactga acccacctta tatgagattc
23501  aaaccttcca gggcatcaaa gaagatagag gcaaaaaaaa aaaaaaaaaa
23551  aaaaaaacta tccaaaggac agcaatttca aagactgaag gaaaatcagc
23601  ccacacagat gataaagaac cagtgcaaga gctctggcaa ctcaaaagtc
23651  agagtgcttt cttacctcca aacaactgca gtagttcccc agcaatggtt
23701  cttaaccagg ctgaaatgac aaaaagagaa atcagaatgt ggataggaac
23751  agagatcact gagattcagg agacagtgaa aacctaatcc agggattcta
23801  aggattacaa caaagtgata caggagatga aagacgaaat ggccacttta
23851  agaaagaaca gaactgatct gatagagctg aaaaactcac ttcaagaatt
23901  ccagaataca atcacaaata taacggcaga atcgatcaag ctgaggaaag
23951  aatctcagag cttgaatatc gcttctctga aataactcag tcagacaaaa
24001  ataaagaaaa aaagattaaa gaagaatgaa caaaatctcc aaagtatggg
24051  attatgtaaa gacaccaaat ctatgactca ctgatgtccc tgaaagagag
24101  ggagagaaag caagcaactt ggagaacata tttcaggata tcatccatga
24151  aaattccccc aacttcacta gagaggccaa cattcaaatt gagaaaatgc
24201  agagaaccct tgtgagatac tatacagata accatcccca agacacatac
24251  ttgtcagatt ctctaaggtc aaaacaaaac aaaaaatgtt aacagcagct
24301  aaagagaagg ggcaggccac ctcccaagga aaccccatca ggctaacagc
24351  acacctttca gcagaaactc tataagccag cagagattga ggacctatat
24401  tcagcattat taaagaaaag aaattccaaa caagaatttc atatccagcc
24451  aaactaagct tcataaatga aggagaaata agattctttt caggcgagca
```

FIGURE 1I

```
24501  aatgctaagg gaattcatta ccatcagacc tgccttataa gaggtcctaa
24551  agagagtgtt aaatatggaa aggaaagatt attactggca actacaaaaa
24601  cgtgcttaag tacacacacc attgatgcca aaaagcaacc acacaaacag
24651  atctgcataa taaccaatta acaacacaaa acaggatttg atccttcaaa
24701  tccacacata tcaatattaa ccttaaatgt aaatgggcta aatgcccaat
24751  taaaaggcac agagtggcaa gttggacaaa gaagcaagac ccaacagtat
24801  gctgtcttga atagacccat ttcacatgca gtgacgcaca taggatcaaa
24851  ctaaagggat ggagaaaaat ctaccaagca aatggaaaac agaaaaaagc
24901  aggagttgct attctacatt caaacaaaac agactttaaa ccaacaaaaa
24951  tcaaaaaaga taaagaaagg cattacataa tggtaaaggg ttcacctcaa
25001  aaggccagac ttaactatcc taaatagata tgcatccaaa acaggagcac
25051  ccaaattcat agagcaagtt tttagacacc cacaaagaga tttagataac
25101  cacacaataa tagtgggaga ctttaacatc ccactggcag tattagacag
25151  gtcattgagg cagaaaacta acaaagaaat tcaggacctg aatttgacac
25201  ttgactaaat agacctaata gacatctaca gaaatctcca cccaaaaaca
25251  ggagtgtata tattcttctc atctgcacat ggcccataat ctaaaattga
25301  ctaatcagcc ataaaacaat ccttagcaaa taaaaaaaaa tcataccaac
25351  cacactctca gactacagtg caataaaaat agaaattaat ggaaattaac
25401  ctgcttctga atgacttttg ggtaaacaat gaaattaagg tagaaattca
25451  gaaattattt gaaactaatt agaacaaaga tactacatac cagaatctct
25501  gggacacagc taaagcaata ttaagaggga agtttataga gctgaatgcc
25551  tacatcaaaa agttagaaag atcttaagtt aacaaccgaa catcacacct
25601  agaggaaata gagaaacaag agcagatcga ccccaaagct agtagaacac
25651  aagaaatcaa aatctgcact aaactgaagg aaattgagac gcaaaaaaac
25701  atacagaaga tcaatgaatc caggacttgg ttcttcgaaa gaataaataa
25751  gatagataaa atgctagcta gactaataag gaaaaaaaga gagatcaaaa
25801  taaacacaat cagaaatgac aaagggatgt taccacctac cccacaaaaa
25851  tttaaaaaac cctcagagac tactaaaaac acctctatgc acacaaacta
25901  gaaaacctag aagaaatgga taaattcctt gaaacataca accttccaag
25951  attgaaccag gaagaaattg aatcctggac agagaccaat aatgagttcc
26001  aaaattgaat cagtaataaa aagcctacca accagaaaaa gcccaggacc
26051  agagggattc acagctgaat attacaagaa gtataaagaa gagctggtac
26101  cattcctact gaaactattc caaaaaacag aggaggaggg actcctccct
26151  aactatgaaa ccagcatcat cctgatacca aaacctggca gggacacaac
26201  aacaacaaaa aacaaaactt caggccaaat ccttgatgaa catagatgca
26251  aaaattctca ataaaatcct agtgaaatga atccagcagc acatgaaaaa
26301  gctaatccac cactatcaag gaggcttcgt ccctgggaca caagtttggt
26351  tcaacatata caaatgaata aatgtgattc atcacataaa cagaattaaa
26401  aacaaaaacc acatgatcat ctcaataaat gcagaaaagg cttttgataa
26451  agttcaacat cccttcacgt taaaaaccct caacaaacta ggcactgaag
26501  gaacatactt caaaataata agagccatct ataagaaact cacagccaac
26551  atcacagtga atgagcaaaa gctggaagca ttcttattaa acaccagaac
26601  aaaacaagga tgtcctctct caccagtcct tttcaacata gtactggaag
26651  tcctggccag agcaatcagg caagagaaag atataaaagc catctgaata
26701  gaggggaagt caaactgtcc ctgattccag tcagtatgat tctatgccca
26751  gaaaacccca taatctctgc tccaaagctc cttggtttga taaacaactt
26801  cagcaaagct tcaggataca aagtcaatgt acaaaaatca gtagaatccc
26851  tgtgcaccaa caacatccaa gctgagagcc aaatcaagaa tgctatcccc
26901  caagcctgcc accatggcca cctacaaact ggtgcagatc cagcacagcg
26951  agagtgagtg gaacctggag aaccacttca gcggctggta cgacgccatc
27001  ctgagcccag cgggccatga ggcggcaaag caggcactgc gagatgctgg
27051  ctatgagttt gacatctgct tcacctcatt gcagaagaga gcgatcccga
27101  cctttctggac agtgctagat gccattgatc agatgtagct gccaatagtg
27151  aggacttggc gcctcaatga gcagcactat ggggctctag ccggtctcaa
27201  taaagcagaa actgctgcaa aacatagtga agcccaggtg aagatctgca
27251  ggtgctccta tgatgtccca ccacctccga tggagcccta ccatcctttc
27301  tacagcaaca tcagtaagga tcacaggtat gcagacctca cagaaaatca
27351  cctaccctcc tgtgagagtc tgaaggacac tattgccaga gctctgccct
27401  tctggaatga agaagtattt ccccagatca aggaggggaa atgggtactg
27451  actgcagccc atggcaacag cctctggggc actgacaagc atctgaaggg
27501  tctctctgaa gaggctatca tggagctgaa cctgccaact ggcattctca
27551  ttgtctatga attggacaag aacttgaagc ccatcaagcc cagcccacgc
27601  agttcctagg ggatgaagag accatgtgca aagccatgga agttgtggct
```

Phosphoglycerate mutase, processed pseudogene

FIGURE 1J

27651	**gcccagggca**	**aagccaagaa**	**gtga**aggcca	gcaaacaggc	accctccctg
27701	cccattgcat	ccatctgtcc	ctccctcctg	aacatgtcac	actgaccaca
27751	tctatagaca	tcttgagttg	cagctgcaga	tggggaccgg	tggctcccat
27801	tttcatttta	gccattttgt	cttctgcacc	cactcccttc	atacattcta
27851	gtcagaatag	cacttctagg	gcacaggttc	tcagtctaag	ctgtggaaaa
27901	gcccccgtta	tccaagagag	ttcaaagata	gtgacttggg	tttttgcaag
27951	tgctttgttt	actaaggact	tgtgaggagg	agccatgctg	agctacgacc
28001	aatgaggaga	agcaagagag	cctgtctgcc	cccaggagct	agtcctgtgc
28051	ttgtctgtag	tcaggccact	gcctgggggc	tctagtcatc	ccagtggaag
28101	atgaatgtaa	cctgcatggt	gatgtgacag	ctgtttcctc	cctgacccca
28201	ttacatttac	ttttatttaa	aaaaaaaaaa	gtatagtgta	tataaataat
28251	acaaaacaat	aacccttcta	agggtttctc	gtggtggttg	aaatagtccc
28301	acatgtggtc	atcagaacat	aagccattcc	tcataccaat	atggggtaag
28351	ctccttgacc	tttgaggggc	aggagtgctt	catgctgtgt	gttttagaat
28401	ccctccctgc	cttgtttcat	ggcagtgaaa	tgcctcttgg	tcctctccaa
28451	gtgtgttttt	cactgatttc	tgaatcatgt	tgcagttgct	tggccctgcc
28501	acataggtct	agtgttcatt	tgagcataac	tgtactaaat	ccttttcca
28551	gatcagtata	ataaaggagt	gatgtgcaat	aaaaaaaaga	atgccatccc
28601	atgcacacca	gttagaatgg	tgatcattaa	aaagtcagga	aacaacaggt
28651	gctggagagg	atgtggagaa	ataggaacat	ttttacactc	ttggtgggac
28701	tgtaaactag	ttcaaccatt	gtggaagaca	gtgtggtgat	tccttaagga
28751	tctagaacta	gaaataccat	ttgacccagc	catcccatta	ctgggtatat
28801	actcaaagga	ttataaatca	tgcttcttata	aagacacatg	cacatgtatg
28851	tttattgcag	cactattcac	aatagcaaag	acttagaacc	aacccaaaag
28901	tccatcaatg	atagactgga	ttaagaaaat	gtggcacgta	tacaccatgg
28951	aatactatgc	agccataaaa	aaggatgagt	tcatgtcctt	tgcagggaca
29001	tggatgaagc	tggaaaccat	cattctcagc	aaactatcac	aaggacagaa
29051	aaccaaacac	cacatgttct	cactcatagg	tgggaattga	acaatgagaa
29101	cacttggatg	cagggtgggg	aacatcacac	actggggcct	gtcatggggt
29151	gggggggaagg	ggggagggat	agcattagga	gatataccga	atgtaaatga
29201	caagttaatg	ggtgcagcac	accaacatgg	cacatgtata	catgtgtaac
29251	aaatctgcac	attgtgcaca	tgtaccttag	aacttaaagt	atagtaaaaa
29301	aataaataaa	taaataaaaa	tttaaaaaat	gaataaaata	catagaaata
29351	cagctaacca	ggtaggtgaa	agatctctac	aacaagcatt	ataaaacact
29401	gctcaaagta	atctgagatg	atataaacaa	aaggaaaagc	attccatgct
29451	catggatagg	aagaagcaat	attgttaaaa	tggccatatt	gcccaaagca
29501	atttacagat	tcagtgctat	tcctatcaaa	ctaccagttc	ttcacagaat
29551	tagaaaaaaa	aattatttaa	aaatttgtat	gaaaccaaaa	aaaagcctga
29601	atagccaagg	caattctaag	caaaaacaac	aaagccagaa	gtatcacatt
29651	gtgtgacttc	aatctatatt	acaaggctac	agtaaccaca	acagcatggt
29701	actggtacaa	aacacataga	ccaatggaac	agaagagata	gcccagaaat
29751	aatgccacac	acaaaccatt	tgatcttaaa	caaacctaac	aaaaacaagc
29801	aatgggaaaa	gaaattccta	ttccataaat	ggtgctggga	taactggcta
29851	gccatatgca	gaagattgaa	attggacccc	ttgtttatac	catatacaaa
29901	aatcaactca	agatgggtta	aaggcttaaa	cataaaacct	aaaactggcc
29951	gggcacggtg	gctcacgcct	gtaattccag	cactttggga	ggccgaggca
30001	ggcggatcac	gaggtcagga	gatcgagacc	atcctggcta	acacggtgaa
30051	acgccatctg	tactaaaatt	acaaaaaatt	agctgggcga	ggtggcgggc
30101	acctgtagtc	ccagctactc	gggaggctga	ggcaggagaa	tggcgtgaac
30151	cccgggggc	ggaggctgca	gtgagccgag	atgctgccac	tgcactccag
30201	cctgggcgac	agcgagactc	cgtctcaaaa	aaaaacaaac	ctaaaactat
30251	aaaaaccctg	gaagatgacc	tgggaaatac	cactctggac	atataggacc
30301	tggcaaagat	tttatgacaa	agacaaaagc	gattgcagca	aaaacaaaaa
30351	ttgactaatt	ttgtcaatta	aactaaaggg	atctaattaa	actaaacagc
30401	ttctgcacag	caaaagaaac	tatcaacaga	gtgaacagac	aacctacaga
30451	ataggagaaa	atatttgcaa	actatgcatc	tgacaaaggt	ctattatccg
30501	gaatctgtaa	ggaatttaaa	caaatttata	agcaaaaaaa	caaacaacac
30551	cattaaaaaa	tgggcaaagt	ccttgaacag	acacttttaa	aagaagacat
30601	acacgtggcc	aagaagcata	taaaaaaatg	ctcaacatta	ctaatcttta
30651	gagaaatgca	aatcaaaacc	acaataagat	accatctcac	aaaagtcaga
30701	atggctatta	ctaaaaagtc	aaaaaataac	agatgctggc	aaggttatgg
30751	agaaaaagga	atgcttatat	actgctggtg	ggaatgtaaa	ttagttcagc
30801	cggtgtggaa	agccgtttgg	caatttctca	aagaactcaa	aatggaatta

FIGURE 1K

```
30851  ccatttgacc cagtaatctc actattgggt ttattctcaa aggaatgtaa
30901  ctcattctac cttaaagaca tatgcactca tatattcatc acagtactat
30951  tcacaatagc aaagacatga aatcaaccta catgcccatt gatggtggat
31001  tggataaaga aaatgtggta catatacacc ataaatacta cacagccata
31051  aaaaagaaca agatcatgtc ttttgcaaca acatggatga ggctggaggc
31101  cattcaccta agcgaactga cacaggaaca gaaaaccaaa tacacatgtt
31151  ctcacttaca agtgagagct aagcattgag ttatatggtc acaaacaaga
31201  gaacaacaga cgcgtaagcc tacttgagga tggaaagtgg gaggagggag
31251  agcataaaaa aactacctat caggtactat gctttttacc tgcgtgatga
31301  aataatctga acatcaaacc cccataatat acaattcacc tatataacaa
31351  acctgcacat gtaccacaga acctgaaata aaagtttaaa aataaatcat
31401  aaaataaaat gttgaaatgc ctagaatgtt tcatagcatt aaattagacc
31451  atgctgtctt aaatgacatc ttatttttcat agaaatcatg tttctgcttt
31501  ttctgttttt ctatgaaaat ttttttaaca agcagaagtt aacgaaatgt
31551  atattttacc acttgggtca agaaacaaat gaaagtattg cccattaagg
31601  agcagttctt catactgtga taaatgaatg taagtattat gtttacatag
31651  atgaagtata aagagaccaa ttaatgtaaa aagccaatac tgtacaaatt
31701  cctgaaggac cattatttaa atctaacttt aatttttaga aagtccttat
31751  tcaagcaaac tttactgaga ccaatactaa ttatactttc ctgctaaaag
31801  atacagataa tgacattagt tagagcctta aagtactact ccaatggaat
31851  aaaatattta aaattgccac caagacccag tggtgcttta tagagagttg
31901  ggtccaatat tcatggttct aatgtgatct aaaaagaagt cgtttgttct
31951  ccttaattca acacctctca gaaattgccc tattcttaaa actattctct
32001  aagactactt ttcctccaag actctgccaa atgtctcccc ttggatcttc
32051  caccataacc aacaaaaaca ttatttttctc aaagttagaa acaaccctgt
32101  gtggccaaaa tatatgaatc ccaacttcat tctcactctg gttgtaagaa
32151  atgctggaat aattaattac tcatttggaa aaaattaaag ctgtatccat
32201  atctatctta ccagattcca agataaactc caaataaatc aaagatttaa
32251  attaaataag accataaaat actgggcaga agaaattggt aaactctctt
32301  agaaccttgg aatctggaaa gattttctaa ttataactaa aaatacaaaa
32351  gtcataggag aaaatattga tagaatacat aaaatcaaag aatactgtat
32401  gataaactaa acagcaacgt caaaagacaa atgtggaaaa atatttacaa
32451  ctcctactaa aaaatagaaa ctaatcacct taaattataa ggagctctag
32501  aaatcaagaa aaacccaaca acctaacaga aaataaaatg gatatgaaca
32551  gactggtcac agaataagaa atacatatat acctcttaaa catacccagt
32601  ctcactcata aaaaagaaat gcaaatgaaa gcattctctc acctatcaga
32651  ttggcaaaaa tctgcagttt gaccacacac tttattgatg agactgcaag
32701  gaaataggca ctcacatgcc acaggagtgc aaaggggtat caccettatg
32751  gaagagtgtc aatatctacc aaaattactt aagcatttac tctttgaccc
32801  aggaagtcta cttcctaata atttcatcaa tttgtagtaa atgttcacta
32851  tagctgaata aactattgta aatccaaaca ataaaatаca gtggaagacc
32901  tttctgcaca gctacagaag aatcccaaga tatatgaaat aaaagaaaaa
32951  tgaaatgtaa tactgcatat atagtgtgct acttttgtgt aagaaaggag
33001  aaaaataaaa gttgactttc atattgcttg tgtttgtata aagaaacatt
33051  gaaataattt ttacaaaaag aagagaataa aaatgtttaa ctgaggatag
33101  cgaatgagga cagcatgaat ggaaacgggt aggagtaaga tttttcagca
33151  tttacctttt tatgtcattt tgatgtttaa aatataaata tgttaactat
33201  tcaaaaacta aattaaaaga attattgcct ggcacagatg aagtacagtt
33251  tagatgttga ctattattat ttttgtatag caatatttgg atgggttaat
33301  gggctcatat tatgtacagt tgttccgaat ctactcacac tccaggcact
33351  tttgtcattg caaagaggga caatgccaaa gataatttac cataggattt
33401  ccatgtgcac ctcctcagtt ctaggctgaa gtaacataga atggcatttt
33451  taactcacga aaaactctgt tctaaaaggt gctttattat ttgccttaat
33501  ttgctcttca tatatttcct taattttaaa cttagaattt tagttgtaac
33551  ttttcaaagg attgcccaag aagatgcaat gagatgatac atgtaaagtg
33601  cttagcttaa tgcctggtgt ttaatcaata ctccataact cttagtggta
33651  gcaaacagaa tcataaaagt gatgtgttca gtgaagcctc taatcaatcc
33701  tagaatcgat acctacaatc agaaaaaaat tatcaactca gaccatcttt
33751  gtatgttttt gtttattatt tttcctcaaa atatcttcaa taaggcattc
33801  ctagaatttg agagtctgtg tatcttaaat aagaatgcat tttattttaa
33851  gaggtaaatg gaaggagcaa gaaccaagac aggtactttt tgagtctgga
33901  gtccttagat ataataagta atttcaggaa tggtatgtat ggtacctaaa
33951  ggatgtggtt taattagaag ggcttttgaa gctttcttgt agactggttg
```

FIGURE 1L

```
34001  ttcattatgg cttcatctat gtttctccca gaaggcttcc ctggcctctt
34051  aactaagtta attgtccctg caatgtgctc cttgtatttc ttctgtcata
34101  atattcatca ctcatgattg tggttactcg attcagcgtc ttctatgcaa
34151  accatgcttt cagccttgtg cagacagaag gcatccatct ggtccacacc
34201  agccatgccc tttaatatta tatgcccagg tcctagaagt ttctggccac
34251  aatgaatgtg tattgaatga ataaaaaatt gagaaaactg caagctagta
34301  aacagtcaca tgagaagcgt catcccccgg gcccccatca caacccctac
34351  acacacaaag taaaaacaac acagtcaaca tgagcaaata gagaaaaaaa
34401  atgtggcaat tattcaagca atgcaaggtg aaaaatagcc cctttgcctc
34451  agttatcaga ggttttcaaa aggatatttt ttgcctgcat tttttaatct
34501  aattgcttca attattttat ttggtcatgg gaacatgatt atatttttta
34551  ataaagtgct taatttgcat gcatgctttg aattgtaggt tcttttacag
34601  gaggcttgtc tactcccata ttgccttttt ctcaattatt ttacttctgc
34651  cttttgcaaa atgttttaaa tatttgattt tagcccctac cacagactcc
34701  aaatctgtgc ttggaatttg gagatcaaag tactgtagct aatccttagg
34751  acatttgcca ttgtgtgact taagaatcca tctcttatca agtttctgtg
34801  gttttctgga gtatttacag gtcacaatgt caaaatgtgc acatctgaaa
34851  ctatttttga attatgcttt ctttatactc ttccatattt agttaatggg
34901  aaaatatcca gctcctgaat ggtattgaac tcgattaggc catctccagt
34951  ctccttataa aagattccta agttgtagta tcacatgttt tcaataaacc
35001  ttgtttttgt tctcctttaa acagagcgtg tcttattcaa aaagctcatg
35051  acagtaggaa aggaattgat aatgaaaaga aagtgagtcc gaaggaggat
35101  ttttcctcat agctttagga tttgttataa gacaatgtgt ttcaccgcct
35151  gacctgcagc ttcaggagtt ggttgccatg aattctgatc ctgtttctgg
35201  aagtaattta tcgcattatc ttgtacaagc ttctctggga cactctttct
35251  ttccttttaa gcacagataa gagcagcaat acactttgca gcgttcataa
35301  acagcaatac ataaaagtaa atatgaaatt agaaagttcc aaaaactgct
35351  ctaatctagt gccagtgagg gaaaattttg gtaaggattt tataagtaaa
35401  gatgggagtt agatgcataa ttatatgtga cctgtttggt taataatccc
35451  actgaaatac agatagatga tagatagata gatgatagat agatagatag
35501  atagatagat gatagataga tagatagata gatagataga tagatagata
35551  gatagataga tgatagatag atagatagat agatagatag atagatagat
35601  agatataata gatctacaca tggcaacaag caagattttc aaaattataa
35651  tgaatgtcag gtatttattc ttggcttata tttactcaaa ttcactcttt
35701  aaagtgctat ctttttattc ttcacaggag gaaaagtcta ttttcacacc
35751  ccaatgttta cccctaagga ttagccaagt gcctaaactg tatccatttc
35801  atatttccaa aaataggaaa ttgtgcattg aaaaatattg agagccaggt
35851  gaaccaggta attctaaatt ttcccagata atacttagaa tgaattccca
35901  tccataaatg tcctttgcta agtgacgttt catctcaagt ggcatctcca
35951  ttgtaacatc cgagtaacac agtctattca aagaacttcc tgaagatatc
36001  ctttcaaaaa cttttagcag taggtgatga ttaatcataa tctgtatgtc
36051  atctgaaaat aagtatcaag tttcttaaag aaaaattaca tatcccaaca
36101  ctactaaaca taactggctg ctaagtttca gagggtccat atcatttaac
36151  tgcttagagt aagtgcaaaa agggagtatt ataaattagg tattgtagtt
36201  ttgctctgta aatttaaacc cataatgcca ttgtttggct gttgatgttt
36251  aaatattcaa gctatgacct tgaataagat atccaagcat ggaatttcat
36301  cataggatgt tgggatttcc agcagatgtt tcaaatttga ttattcattg
36351  gtggaatcca aatcttttct tttttaatct gcagtcaaat actggtatgg
36401  ggttctgttt agaaatcaaa actgactgca gctttgtcat ttggtatgtg
36451  tgaaaatagg tactgaagaa aattttaaac atctgatggt atcaacgtgc
36501  aaaattgctg ttcctaaaag ctgtctcaaa ctttctatat aaaagaatat
36551  aatataaagc cactgtatca ttgccctaaa ccatgttcta aagcatcaga
36601  aaatacacat gacttttcat ctcttcgatt tattgaaaac tgatggaatt
36651  acacctaggt aatttactca agatactaga ctatgcctta aataggatgt
36701  gcctcctact cattcatgat gactctcagg ggacaaatgc ttctttcctg
36751  ttttataaat acagaaacac agcttcctta cctccttcag tctgtaaccc
36801  acatctgaaa ttaaatgttt gtgatcacac tttgaagcaa tttgtttcag
36851  taggttactg atattgcaag ggattcgtcc tgtagcatga aaaaaaaaaa
36901  aaaaaatcta ctgcctgact ctgcatccct gacctttccc ccagactcca
36951  gccccattca ccatctacca aatgcctact agccatctca aaattaacat
37001  ggccataacg gacaagtagt tctgcccttc aaatagtgct cctcacctat
37051  ccccagtggt atttccccag cttagtaaat agcactttat tcacctgatt
37101  gcttagacca aaaaccctga agtcagcctt agactccctc gtttgtctca
```

FIGURE 1M

```
37151  tcccacagtc agtccttcag caagtcttgg cctctccacc ttcacaatgt
37201  gcaccaaatc cagctccttt acagctcctc ctgactttaa cctcactctt
37251  gtaatgctgc tctcaccctt tgtccagacc acagcagtgg cttcttacct
37301  ggccttccag cttcctctct gacatctggc ttcctttctg gcatccagcc
37351  tcttcctggt tggtttccca aaggtaacca aaatgatctt gtaaaataca
37401  catctgatcc tgcactctgc caaaaaccct ttccctgccg ctatcatata
37451  atacttagaa ggacatctaa agctattccc aaagctgtcg tgatctggct
37501  ggagccttct ctcactccgc tcaagctaac ttgatctcct tgccttccct
37551  tgaacacact gaacacactt ccacctcaag gtctttttat attttttgc
37601  ctggaaccat ttttccttag atatgatcac ggtcacccct tcacttcgtt
37651  gggtcatggc tcctctgaga tgctttccca ttgagacaac cgaaaatact
37701  aaaaacggcc gggctcagtg gctcacgcct ataatcccag cactttggga
37751  ggccaaggtg ggtggatcac ttgaggtcag gagttcgaga ccagcctggc
37801  caacatggtg aaaccccatc tctcccaaaa atacaaaatt agcctggagt
37851  ggtggtgcac acctgtaatc ccagctactt gggaagctga ggcaggaaaa
37901  tcgcttgaac ccgagaggcg gaggttgcag tgagctgaga tcatgccatt
37951  gcactccagc ctgggtgaca gagactgtct caaaaataaa ataaaaacta
38001  aaatattaaa aacatgttaa ttataagatg tttgctaaat tttacctgaa
38051  tatcaaccat ttgcaagtag ttatattccc tattcttaat aatactttac
38101  ttcttggaac ttcacattaa gatagagcac ccgcccctct gtgactccac
38151  cctcatcctg ctctgcattt ccccagggtt tttgtcacta cctaacatta
38201  tattctgtac ttgtttattg ctttaacatc agcctacccc aggtgaacat
38251  aagctccatg agggcagaaa actcttctct tttattcact gctctatacc
38301  tcatgcttgg cttatagtag acatgcaaca aaaaatattt gtcgaatgaa
38351  ctaatgaatg aataaataaa ttgccttaac acttaatttg agaaaagtca
38401  tatccaaaac actccttctg atgcttcctc gttcaaccag tatccaaaac
38451  aaaaaatgta ccacttagaa tttgagaaat tcaaagttag aaaggatcct
38501  tgagacttgc cagttcaatc caactatttt aaaggtatgg aaaccagccc
38551  tgagagataa gtggtgacaa agctagttaa tggcgaacag ataattaaac
38601  taggcatagt tcaatgttct ttatgcttcc atgctttaca tctctgtttc
38651  ttttgaaagt tccttctgta tacataagca aatataatgg aaccagaaca
38701  cttctattcc ttcttatctt gctgctctgt tggcaataaa acatctggca
38751  catgatatac atgggacact aaaaaaatta taaatttctg cagaaaaggg
38801  ctcacattga taaggcagat tgacctctct gtctcaatct gctgtcccat
38851  tgggacaacc taaaatataa aaaacatgtt aattataata ttttcactaa
38901  attttacctg aatatcaact atttgcacgt agttatattc cctattcttg
38951  ataatacttt acttcttgga atatcacatg taagcctttg cttgactttc
39001  tacatccctg tttactaggc tttctatgac ataaaagcta ccaaaagaga
39051  aacacgggaa aaaaatatat aagtgctctg gaaacagaaa ttagtttgat
39101  ttttggctcc atttaccagc taaatgactt tggataagat tcttggactt
39151  tcttagtatc aaattactaa tctagaaaag tgaagggaaa ggtatatcta
39201  taaaacattt ttttttagat tgagagttaa catgatacca ggcacactaa
39251  ggcagactaa aggctttata tgtattattt catttaatca tcccaatagc
39301  cctgtgagaa aaagggatct attccctatt tgcaggtgag gactccaaga
39351  ctcagcaaga ttaataggcc caaggtcaca caactaagaa aggacagaac
39401  tagaaatacc tgggctgttg cacatgaagt ttatactcat aacctctgtg
39451  cctccttgaa gggctattat ggagaaacaa tgaaataaag tctgtgtact
39501  gagcatcccg cacagcctca tatatcagag gtactcaata aatgttgccc
39551  atttctcttc tgttttccca ccactgacta aataaattac cttggccaat
39601  gtactaacct ttctaggcca tagcttcttt tttaaataag ttatggttct
39651  ctttttttctc attacaaaag caatacatgg ctattaaaga tcatttggac
39701  aaaagatata tatatatata taaaactaaa atttgtacgg aatcttacca
39751  cctaaagata atcaccatta atatgcaaat gtatgtattt atactattta
39801  tttttctata tactataaga atacataatc tggccaggtg caatgactca
39851  cacctgtaat cccagcactt taggaggcca aggctggtgg atcacttgag
39901  gtcaggagtt cgataccagc tcgaccaaca tggtgaaaca tcgtctctac
39951  tagaaataca aaaattagtt gggcatggtg gcaggtgcct gtaatcccag
40001  ctactgggga ggctgaggca ggagagacac ttgaatccta gaggtggagg
40051  ttgcagtgag ctgagattgc gccattgccc tctagcctgg gcaaaaagag
40101  ggaaactccg tctcaaaaaa taataataat aatacataat attttgggag
40151  agcaaaactg aaatcctgct atcctgctat gtaatcagtt atttaaataa
40201  tgatgtttag aaacatttta tctcacaata ttcttctaag acataatgtt
40251  ttgtggctgt atcgcatttg tggtaataat aatagtaata ataaattagc
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```
40301  tcaaatgtat gttagtattg tactgagatg tttcacagtt aacttattca
40351  attcttgcaa ccctatgaca taggtacctt tattatctac attttacaga
40401  taaagaaact gaggcacaga aagattcagt cacttaacaa ggtaacccag
40451  ctattaagca gcagagccag gattggaact gaggcacatg agcaccacag
40501  cccatgctct ggaagggata tagcatgttg ttttttatta atccatcctc
40551  attagaaatc tggattggtt ctcatttttt atactgttac taatagtgtt
40601  aggtatgagc tgggaggaga aaaaaacaat agtttaataa gtatgctgct
40651  gcaaacttgt taacatctac aattttatca tacatcccta cagtttaaat
40701  tcctgaaata agttattcac attgttaatg gttttgtcaa ataatgtcaa
40751  attgctcccc caaaaaatac cataccaatt tattcttaca gaaaatcttc
40801  atcaaataac tttttttctc tgccttgcca acattgacaa ttcatttttt
40851  taaactttgt cagtttgata gaataaaatg gtacctttct agtattttaa
40901  atttcaaaac tagaaattgt aaagaacttt tctatatatt aattagtcat
40951  tgtttcttct tcctaggata aattcgtcta tgtgccttct gtccaatttt
41001  ctactagcat gttttcttag tgttttatgt ttatatatta aagatattaa
41051  tcttttgttc atcatcatat atgttgccat ttttttccag gtttgttttt
41101  tgcatttcaa tctgtgtaga gttcttttct aatgtatgga attttcgtgt
41151  gttcgtgcct tcacttcttca actgcaaaat atgggagatt aaactatatt
41201  gtttttaaga cctttaaaat tataacattg tattctattt ctttcctaat
41251  tactacaaac aaataactta tcaggtaagt atctatcaaa taagttttga
41301  acatctacag tatgatatgt acggagctag tcactgaggt tacaaaaaaa
41351  aaagcacgtc tgcatgcagt tggtttctta tagcttacta tagaagagac
41401  cagcaagtaa acagactact agtataatca tgggtaataa gtgttatgac
41451  aggagcatac ctcagacctc tgggcacaag tggccttgac tggttgatat
41501  ctgtgctgag ttccagaagc aagcagaagt gagccaggta aagaagggag
41551  aagggccttc taggcagagc agcagcattt tatagagcac tttgaatgcc
41601  aggtagcaga atttgatctt tcttctatgt attggaaggc ctttttttaaa
41651  tcacagaggt agtataatca tcttaacatt ttcatgtggt agtagaatac
41701  aaagtggttt agagaaagga aaaacaggag agtgaaaacc aggccataca
41751  ttgtagggat gaccaagaga gaagtagcgt agcctgaact aaggaggaga
41801  caggataaat ggaaagagaa aattagatat gaaacatact atggaagcag
41851  aatcaacaaa agtaaaccac tcagtagata tgagacgagg aagacaataa
41901  agaaggagat gttaatccgt gaatttaata tgaggtctgt atcagaattt
41951  tgttgtttaa cttgattcat ttattctgaa attcacttgg taaaaataaa
42001  tacgtttaca ataattgata ctactttgaa aaagaataac atttgtgtca
42051  cacgaatata ggaataggca ataaaacata atagaatccc aaaataggct
42101  tctcaataag tatatgcaaa catttggaga atgacagagt ttttatttag
42151  atggtattgg gaaaattgac tttcatatgg gataaaaagt aagattagtt
42201  ctctacttca ccacagagac aaacaaaaat tccgttaaaa ctaatgattg
42251  tataagttag agtaatgctt agttattata taaatctcca aattctagta
42301  actaaataaa atagaagttt atttcttact tgtgtaatag tccaatgaag
42351  gtgttctttg tttggggttg gggtatatgg taaaggctct gttccatgca
42401  gttattcagg aacccaggct gacaaaggca gtgccatctt cagcacatgg
42451  tttctaaggg cattcttagt accaaactgc aactgacata gaaaaagaga
42501  aagtgataag ccatatgtgc ttgccctcaa ctgggaagtg gcatacatca
42551  tttccattcg tcttcattaa ctagaattag tcacctcatc tcacccagaa
42601  gcaaggggtc ccgggaaatg agacctctag atgggcaacc acttctcaga
42651  gataatgctg taccttagaa gggaagcaca tatctgtggt agacagctag
42701  ctacctttac cacaaagact attctgaata gtaaacataa attcattaac
42751  taaataagga tgtaagtgtg ccaaaataaa atataggaaa atatttttat
42801  aatcttggtt ggacaaagtc attctagata acttaacttc tgtgacttaa
42851  aaatgacatg aaatccaggc atctaaaaca ggaggggat ggttttgttt
42901  ttcccactgt atttgcaaag attgaagact tataatatcc caggtaataa
42951  atgagtgtgc ttagaaccat gtctatcaca tagtgaacag taaacattag
43001  atttactagt actattttta ttattattag cattcctttt tattagcaag
43051  gagagagaaa taagtgtttc catacattgt tagtgagaat tggtaccatc
43101  attttgaagg catcttgata tcaatcacaa atcaaaatat gccaagaatt
43151  cagtctcaag aaatttagcc ttaaattcct tatcctaaaa ataaatgtac
43201  aggactattc gtttcagcat cattttaata gcaaaaccaa aagtaaccta
43251  aaaattcatt aataagtgtc ttagtctatt tgttttataa taaaggaata
43301  cacaaagctg ggtattcata aagaaagtag gtttatgtgg ctcacagttc
43351  tgcaggctgt acaaaaagca tggtgcctgc atctgctcct ggtgagaacc
43401  tcaggctgcc tccactcatg gcagaaggtg aagtggggcc aacatgtgct
```

FIGURE 10

```
43451  gagatcacat gacgagagat gaagcaagac ataagtgcca ttttcttttt
43501  aacaaccaaa tcttaaggga acttacagag ccagaactca gtcattactt
43551  caaggacggt accaagccat tcatgagcga tcctccccca tgaccaaaac
43601  acctcccatt aggcttcacc tctaacactg gggatcacat ttcaacatga
43651  tatttggagg tcaaatatcc aaactatagc ataagtaatt ggttaattaa
43701  ataaattagt gtcctacctt atatacattt gtattgtttt gatattttac
43751  tttataactt taaagtgtat attttattaa aattattcaa aacttagctt
43801  atagtgaggc cactagaata attcaaaaaa ctggaacaaa aaaatgtggt
43851  gggagagggg gatataaaca tcaagaacat tgtatttgtc gtacttctga
43901  ttgtctcaga gagaacaaga tgaagtgagt ttaaagggaa agaggtaaat
43951  ttatgttagt tattagggaa aactttctga gactatagaa taacttttaa
44001  tttacaaaaa ttttaaaagc ctgaagtctc cagacagttt ctagaagtca
44051  agatataccc tctttgtggc ttacttacct cgagagggtt tatctgtcct
44101  tataactact agtttgaaag tgttcaacca tgctttgttt gatccagatg
44151  atttagttct tttcattgtg attttacatt gagccatgtt atactttcta
44201  atacatgcat tatgcagtgt aattgtagca acaaaacaca gtccatcagg
44251  ttcagatgta caattggcct tgctctaacc caatccttga gttcacaata
44301  gggaagcttt ggatgtaaat aatgaaggct ttttggtatt tcagtgacta
44351  acacctttta gacagggtcc atggtgatca attcatattg attttgctga
44401  ctaaataata cttgagcaaa gttccagtgg catctaaaaa taagctcttt
44451  cacagtcctt atgtgtctta aatatcatta tggtatttat tttgttcaaa
44501  tctttgcagt cacctcaaat ttcaagaatt catgtgtaaa tcattctaag
44551  tgatgcagta aattagtgaa cctacttcct aataccttgt aaacctatat
44601  ttcacatttc tactgggctg cttataatca atagctcttt cttcactact
44651  tcccaacttg ttctaatttg tttcctttga gagaggtaga ttttaagagt
44701  tctggattac atgcttttct ttttattcat gtgacttaga gctcctcctt
44751  gtttattagc agttctattt ctttctctag ccccattttc tcttgaagca
44801  gccataaaag taccatctgt ttttcagcat cattttattt ctgctttctc
44851  ctccctgcac ttttctcttc tctgaatgct ttatgcgata acaatttatt
44901  cctgatttat tatccacctg ctttcatagc ctccccctttt ctgttcctcc
44951  tccatcccta tcccaccctg gatggagtgg tataccataa ttcttaagga
45001  cacagctttg gagtcaagta agggccagct caaccactta tgcatgttag
45051  tgacttgacc actatgagcc tcaatttctt catttataag aaagagaagg
45101  ttataatatc atctactaca taggttggct tgaagaatta aataaaataa
45151  tgtacatcag ggtttctcag ccttggcact attgacattt ggggctgagt
45201  cattctttgt tctggaggct gtcctgggca ttgtaggatg gttagcagca
45251  accctagtct ctaccactag atgctcgtag caacccccctt cccagctatg
45301  acaatgcaaa atgtctccag acattgctaa atgtcccagg gaggcaaaat
45351  tgtccccatt cggaatcatt gatgtatata aaacatttag cacagtgcct
45401  ggtacatagt agggacttga tcaataattg tgatggatgg atggtcagat
45451  gaatgattga atattcattt ttaatacaag tgtctaatat aattcttgac
45501  agtcaattaa ctacttaata cataaatgga taaacaaatg aacctgaagc
45551  cagtgagctt caagggctgt ccatagtttc taccttacac caaaatgtgt
45601  tatcttcact aaaaacaagc ttcctatgtt tcaaaaaata ttttagacaa
45651  ttaactaact gcacagctta agctactccc ccaatttaat atatatgcat
45701  atactttaaa taatagggag attttaaaat aaactctaat ggatgatagc
45751  tataacaatt atgttgctat agaattcagt gctagaaatt gaagtgatcc
45801  tttgattaac ctgagtattt taggttgata tcccagtcaa caagccattg
45851  atgtggtaag agaacaaagc tcagccaact tttaagtgtt ttttaatcta
45901  atttatctta tttaaatatt tattgagtgc ctactatatt tcaggcactg
45951  ttctaggtac tcaggataca attgtgaaca aaacaatgat aaaacactgt
46001  ggaaccacca ttctatgaaa tagtagatca caaaaatagt aaatacataa
46051  atagaagtaa aaataaagac tactcataac ttgtaaaata ctagcctagg
46101  aaatagtcta ggtggtactg acagcaaaat tccagtggat gactgtaacc
46151  caaccagaaa catttttgtg actgcactca ctgtttgcca tttggttgct
46201  catctatgat ttcagtttac tgaactctaa ctttctcgtc tgatctgaat
46251  tacaatgagg gtattaaatc aaatctgtgg ttacctttgc atattttgga
46301  acttcaaaca tttagattgt gattcactgt gtgcataatt ttttaaattg
46351  tctcaaatca acaatctttc tcttactttt ctaggttttc tctaatgaac
46401  taactttata gcatactttt tgtgctgtag tctaacaaac cgatagctga
46451  gtttttttaa aaatgaatac aatatatgct ttttctgcct cgctttttttc
46501  atctgtaaaa tgggatctgt gggataccta acacataaag tcattgtaag
46551  gattaaataa ggtaatgttt attaaaaaaa aaaaaaacct tagaactgaa
```

FIGURE 1P

```
46601  gaaaatgcca agcacatagt aagttttaag tgtagtattt tctgcacccc
46651  tactagccat gtacttattt ctagtatttc caatatttta gcatagtaaa
46701  tgaggtagta tatcttttte ttttctttct acacttggga gaaagcagga
46751  ttacaatgaa ataaaagcaa aatgtatgtc caacagggtc atataagtaa
46801  tgtctgtttg taaaccacta gtctcaggag taaatccctc aacatgatga
46851  aaaccaagag atgtgtttgc acataactct ttttataaag ttttttaat
46901  tgcaaagaca tagtcgttgt tataaacttc caacatacag aaattaataa
46951  tttacaaagt gaaaagcccc tttatgcata tattcacttc agctcactcc
47001  ctttagaaat aattaatagt aataatcagc gtatagtctc actttttttt
47051  ttttttgag acgcagtctt gctctgtcgc taggctggag tgcagtggca
47101  cgatcttggc tcactgcaac ctccgcctcc tgggttcaag ggattctcat
47151  gcctcagcct tccaagtagc tgggattaca ggcacgtgcc accacaccca
47201  gctaattttt gtatttttag tagagacagg gtttcaccat gttggccagg
47251  atggtctcga tctcctgacc tcatgatccg cccaccttgg cctcccaaag
47301  tgctgggatt acaggtgtga gccactgcgc ccagcctagt ctcaaatttt
47351  tttcctagtc atatactaat atatatttct attaaaataa aatcacattg
47401  tacatactgt tttgcaactg gcctttattc acttaaaata tgtctttggt
47451  gtcagtgtca acacatttag ttccttcttg tttccaacag ctgccaagag
47501  tggtaactct ctttggctct ctgggtactt acccacaaaa gcacatgcat
47551  ttagagctgg tggaaaaagt ccttcagggc ggacaccggt ggctcacacc
47601  tgtaatctca actctttggg aggccaaggc tggcagatga tgtgagctca
47651  ggagttcgag accagcctgg gcaacatagc aataccccat ctctacaaaa
47701  aaatacaaaa attagccagg cgtgttggtg catgcctgta gtcctagctc
47751  cttgggaggc tgaggtggga cacagaggtt gcagtgagca gagctcatgc
47801  cagtgcactc cagcctgggt gatagagtga gaccctgtca aaggatggaa
47851  agagggaaga aaggagagga gaggggaaga agccctttgg ctgaaacttg
47901  cactgccaac aactgacccc ccctctctct caaagcactg acccaaaaag
47951  gggcaccagc agagaggctc agaagatctt ctcagtccac accaggagac
48001  cagacctttc tcagtgcagg gagaaggatg agctgaatga ggaatactca
48051  cttatacagc agttaatcca gaggatgaca gaaacattac aaatgtgaca
48101  tccttgaaat ggaactcctc tttggagtgt ggaagcccag tcatgcacaa
48151  cccacttgga gcaggaagga aattgtattt gaggatgtta aagtcaagct
48201  aacttttatt aaaattgcca caggaggcca ttcatcccca cttcacttat
48251  cccacttcaa agcctacttc ccatcactca gatgtttact tatggagtga
48301  ttaagttttc ttttatcttt tctatgcttt catcagatgc tctttttctc
48351  ttttttgctt agaaaaggca gatttttttca gcctaatgtc aatatgtcaa
48401  acattaagta ttcattccct tgcaatgcac agtgtttata cttacatacc
48451  ctattataac aaatgtaata ttatttaatt atgcagcaaa cttacacata
48501  attggtgaac aggtctaaag aatactctat acaggaagca tagagtattc
48551  agcttagctg aggcctttgt taaacaatat gcaaagttgc aggtgccaca
48601  ttagggaatt ttgggggaaa ggaaatgcaa acttatttgg caggaaaaca
48651  agagaaatga ttatatctca cagcactttc aagctggaca catttacatg
48701  cctctgtcac atcacccaga agctgtggtg ttgagggctg aggcaggaga
48751  tccttttgcc acaggaaaaa ggatgaaacg agagacattg tgaaaggttg
48801  ccccaaagtc ttaaggctcc ctgaaacctt gggtttttttg aacaccattg
48851  tccaatctgt tgaaggttaa ataatacgtt gttcaaaatt gcataggtaa
48901  agcgcagaat ggccaaaggg tcagaactac agcaataggt aggtcccatt
48951  ctctgccttt tcattcttca gtcttcggaa atgccacaga ggccaagtgg
49001  cactaggtgc agctgggaat caagatctgt ttatctgtac cttaaatagg
49051  tcaaagtgaa ccttttggaa atattgtttt ggtaaataaa aattcctggt
49101  cgtgctaact gtggctattt cgacctgttt ctttcagATA CCATTGTTCT
49151  TATCGCTTCA ATAGCAGTTG TTTCTGCAAA AACTCAGGGT AATATTTTTG
49201  CCACGTCTGC ACTCAGAAGT CTCCGTTTCC TACAGATCCT CCGCATGGTG
49251  CGCATGGACC GAAGGGGAGG CACTTGGAAA TTACTGGGTT CAGTGGTTTA
49301  TGCTCACAGC AAGgtaagat ttgctctctg aatttaaaaa cacaattttt
49351  gaaacttttt cattgatcgc tgtaatagtt aataaacctg tcacaagaaa
49401  acttagtcat tgcagaaaat ggttaaaaca attttgggac atgatgtaca
49451  atggattatt taagagccat cataaacatc caagaagtag taaagtgaat
49501  agaatcctca tagaattctt ttttcctttt tcaaagattt cccacctcta
49551  aaaatctttc attcctttta tatctagGAA TTAATCACAG CTTGGTACAT
49601  AGGATTTTTG GTTCTTATTT TTTCGTCTTT CCTTGTCTAT CTGGTGGAAA
49651  AGGATGCCAA TAAAGAGTTT TCTACATATG CAGATGCTCT CTGGTGGGGC
49701  ACAgtaagta taaaaataca ttttttattt attggatgtt gtgaattgtt
```

Exon 4(A)

Exon 5(B)

```
49751  ttttttaat acaacgtaat ggttcctatg gatggtttca ataaaaatat
49801  taaattgcga aagagagtta tatggaaaat aaatactact tattattgtc
49851  taaaggcttt ccacatcttt ttaggccaac taagttgtct tgtaaaccat
49901  cattaatatt tcttgagtgc tagattgttg ccaaaattaa aaatatataa
49951  aatatataaa tatatatcat ttttaaaatg gtgattaaaa cattgatagt
50001  ttgtttattt gttttaactt tgtggagcac aaatttaaat gatcaattgt
50051  tgcattgatt ttccgctctt caaaagttta tctggggtta aaaaatgaat
50101  ggaagctgtg aataaaattg cagcacaaag aaatgaaaaa gaagactggt
50151  aaccatctgt gagatcagag attatagtca cctaatttca aaactttcct
50201  ctcaaaacct actttttctt tatattatta aagaataatt ttccaaataa
50251  ataaagtaaa atcatgattc ttacatagaa agaaaattaa cacatgctaa
50301  acattcattt aactcatttt aaaagtttaa gtcattatta atgaagaaac
50351  cagtaagatg ttaaaaccag ttcaaagcac tatccaaagg acagaaacat
50401  ttaaagatca ggaatattga aatcaatgtg caaatagagg caaaactggc
50451  tccttccaca gtgtgggagg gaagtcagtt caacctccac taggcagaat
50501  ttatttacat gtccataggc aagaattatt ttgcattgct accagttatc
50551  aacaacttac agagttgtaa aatagctcaa aggctatgaa aagagcagag
50601  ccccataaaa tcagaatcca aaaacctgga agggtgtact ctgaacaacg
50651  catagttttc cactgaagca aaaattttcc ctgcattgta aagaatttat
50701  gaaacagtca ttggagctat gccgtaataa gaatgacatg ggatatagga
50751  gtgctttatg caatgtataa attacatttc tttttatttt attcctttaa
50801  ggtattccaa aggggagtta tatgaaaata atcatagcca aacatggtgg
50851  ctcacgcctg taatccaagc actttgggag gctaaggcgg gccagttgct
50901  tgagctcagg catttgagac cagcctgggc aacatggcaa gaccccatcc
50951  ctacaaaaaa tacaaaaatt agccaggtgt ggtggcacac tcctgtagtt
51001  ccagctacct gggaggctga ggtggcagaa tcacttaagc ctggcaggta
51051  gattataaat gcttgtctaa agaatgtcca tatcgttttg gttcaaaaaa
51101  ccccgtgagt tctcttttaa accaccctta gtatttcttg agttctagat
51151  tgttgccaaa ataaaaatat atcattttct taagctgtga tttaaacaat
51201  gataggcttt ttatttgttt gtttagtgaa gcacagagtt accaattgtt
51251  gcattgttcc actagtcatc aaaagctcat cagcaagacc cagaacattt
51301  gtcagagagg gggaaaattt gttagggctg tatttagcag aacttgttgt
51351  atttgttgat tgcatagcag caataaaatg aataaaaatg agaaatacat
51401  tcacctaaag attcgaattt ttttcttaag ttatctaagt aaatgtctac
51451  aagattatgc cattggtttc aaaggattcc gttggtttaa taatgtggtt
51501  tccggctgct cttcactatt cacaagcaat aatgggcatt tcgaaaaaga
51551  gtggaagctt gaaagagagc agttatctga cattcttaaa atacttttta
51601  tatgtagaga gcaaatgaaa atctgtgact catgatggga taaactgtaa
51651  actgagaaaa caggaggctt ttcttgccag caaggggaag acagtttatc
51701  atcccagcct tcaaagcaat ggtttgaatt caagtttaat ttttgcttct
51751  cttggataat tctaatgtat ttgacttact gaggcaccca ggtgcccctt
51801  ttgccactga gatgcagttg ttggtgagtt tagcctggga gctcattatc
51851  tttcttttta ttagtcttcc atttctcctt attacaaaaa agaattgctg
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51951  gtcatcagtt tgtttctttt gccagaataa cccacacggt aggttttcaa
52001  aggtcatatc tgtgactttc aggggaagaa acattttcat tgatttgcct
52051  ttcagttctg ctaatttgac tgacatttaa cccgtactta acaggttcct
52101  gaatggccta attatgtttc tatttttaaa aaaaatctag tcttgaatat
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52251  tgtctgaatc ctaaaaagac agaagaagca aacaaacaag agagctcatt
52301  gtttctattc attttaagaa gaacatatac tagattccta gtgggaaata
52351  aaataaattt agactattat acctttttatt tatacattaa tcaagacctt
52401  agtgaaaatt atggttgggt atttcttagt taaaattgcg catgttgcac
52451  ctaatggaaa ccttaataac tatggaagta tccagaataa atagggaaat
52501  gatagcatcc taaatgagag tatttctaag tgttacactt tgatgaaaaa
52551  aggaaatccc ctatattaaa agatcccaca gtatcaacat taagtatcaa
52601  aatataggtt ttgttccaca gatacgctgt gccagtgaat tttcaatact
52651  aactctggaa ctccttccat taagatagtg agatctgtcc cctagatcaa
52701  catttggagg gatatcatgg tgggatcagt gctgcccaaa aaactttgat
52751  ccctgaaagc agtttcatat tagtgaatag caatacctag ttcattgagt
52801  aagtgaaata gatataaaag acctggtacc aagaacatag gaagtgccca
52851  atcaaatatg agagctattg ttggtgtaga catcattgct gtggaagtta
```

FIGURE 1R

52901 aatgaaagca cctttaatac aaaaggaaca aaaaaagagt tatgtgtttt
52951 gatgcagacc cacagtttga acacagaaga ggcttgggaa ttggaggttg
53001 tgatgaaaag atgtcctggg ttctgatgtg gcaactaaag ttgcattgat
53051 ggcagaaaat ggaagaggga agtagctcta gtagctgagg cactgagagc
53101 tgctggaaaa ggggatcttc tgattgttgg atagagctcc atttattatc
53151 atttctatt gttatttttc tcatttttgg ttgttccaga tttattctga
53201 aataatttaa gaatgggttt ccctggagtt attttctgtt attaaatcct
53251 tcctgttttg tgggagtgat ttttctcttt ttgatctgct ttagatttat
53301 tttgaaataa cttaagatca ggttttcctg cactccagcc tgggtgcttg
53351 agtgagaccc tgcctcaaag actcccttgg ggagaattat accgtgccac
53401 ggaaatctac caacagtata ttgttcacct gaacacatta gctataaact
53451 aatgtacata gatttactaa aaacataatt gtatcttcaa aatcaggtca
53501 ataaatattt gttgatttgt tgcctgaaag aaagaaggat ttatatctcc
53551 tgatttggaa ttaattctgc tattgaaaag aaaaaaaact ttagcctaac
53601 cagtgtctta aattataatc tgaccatagc ctcagccatc tcatttaaaa
53651 aaaaaatcaa gaaaagtctg gaccagagtt ttcatttgtt tttcagtatt
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53751 ccacctcaga ttttcctaac ataattacaa ctttatgcca acatttccaa
53801 cccacagatt ttcagaatgt attttctttc acctgtgtga ctgtatttga
53851 gcataggaaa cataagggcc aaaatatatc taagctgttt ctatctgcaa
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55951 tcacccatgg gactcaaccc ttgcacccta atgccatatg cacatataga
56001 actggcagag aattacacaa caaagggggc gggatgtgat ggaagtatct

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56051  tcaaaggagc aactacatta tttatttaat gttggattcc cagtctaaag
56101  atagtgtaaa gggattattt atttaatgtt ggattcccag cctaaagaca
56151  gtgtaaaggg agtgtgttat ttatttgttt ttctttataa cagtaatcca
56201  ttttttccaa aatcagctct ggctctttaa cttcatttgg cccatattac
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56901  tcaatgaata tctatgcagc gctcatctaa ggatggttta tcaaatgcag
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59101  cttgctgata gattccgtgg ggggagtgag ggaaatgaat agttaggatg
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```

FIGURE 1T

```
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59351  gagtgtttag cataaaagtg gcatttaaat ctatgagaac atttaagatc
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59601  tagaaagagg tggtcagctg agctgaatgc ttctgaaagg tctggcatca
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60101  gctgagatta caggcataag ccaccgtgcc cagactcact gtccttgttt
60151  tctattaggc tgtgacatca gagattacct ggtctttgtg aaactctcca
60201  ttctctattg agtttccatt tatataaccc tttcccgatt gttctacttt
60251  tgaaaaactt gaaaaacatg acatccaaag acattcttct ctgactttcc
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60351  ctttctgtgt accttttgta atctcagtta tgcacatagc tttaacatca
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60551  ctttactcca aaaccttctc tttttcatta taatgctttt atttatggtg
60601  caaccatctt cccacttaaa attttcaagt cactgttaac ttagtctttc
60651  cttttacctc aatcaataaa tttatttcta ttgaacttcc taaacatttc
60701  cctttactct ccactctcat agtgtcttaa ctggtctctg cacctctcat
60751  ttcttcctat ttcaatctct cctgtacatt tgctgccata atttcagctt
60801  ctaaaagcac tactctgatc acattatgta ctttgcttac aaaaaccttc
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61201  ctgttattat tatacagtgt cccccagcga ttatttttct gtaaattatt
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61301  gtgagatttt ggtgcaccca tcacccaagc agtatacact gcaccctatt
61351  tgtagtcttt tatccctctc ctccttccca tcctttcacc ttgagtctcc
61401  aaagttcatt gtgacattct tatgcctttg catcctcaga gtttagctcc
61451  cacctatgag tgagcacata ggatgtttgg ttttccattc ctgagttact
61501  tcacttagaa caatagtctc caatctcatc taggtggctg caaatgccat
61551  taattcattc ctctttatgg ctgagtagta ttccatcatg tatatatata
61601  tataccacag tttctttatc cactcattga ttgatgggca tttgggttgg
61651  ttccacattt ttgcgattgt gaattgcgct gctataaaca tgcatgtgca
61701  agtgtcttct tcatataatg acttcttttc ctctgggtag ataaccagta
61751  gtgagattgc tggatcaaat ggttctactt ttagttcttt aaggaatctc
61801  cacactattt tctatagtgg ttgtgctagt ttacattcca accagcagtg
61851  tagatgtgtt ccctgttcac cgcatctcca ccaacatcta ctatttttcc
61901  actttttat tatggccatt tttgcaggac taaggtgtat cacattgtgg
61951  ttttcatttg catttccctg atcattagcg atgttgagca ttttttcatg
62001  tgtcttggcc attcatatat catcttttga gaattgtcta ttcatgtcct
62051  tagcccactt tttgatggga ttgtttgttt ttttcatgtt gatttgtttg
62101  agttcattgt agattctaga tattcatcct ttgtcaaatg tatagattat
62151  aacgattttc tcccactctg tgagttgtct gtttactctg ctgactgttt
62201  cttttgccgt gcaaaagctc tttagtttaa ttaagtacca gcaatttatc
62251  tttgttttta ttgcattcac ttttgggttc ttggtcttga aatccttgcc
62301  taactcaatg tatagaaggg tttctccaat gttatcttct agagtgttta
```

FIGURE 1U

```
62351  tagtttcagg ctctatattt cagtccttaa tccaccttca gttgattctt
62401  gtatgtggtg agaaatgagg atccagttta attctcctac atatggctag
62451  ccaattatcc cagcaccatt tgttgaaaag ggtgtccttc gcttctcaaa
62501  agaagacatt tatacagcca acaaaattat gaaaaaatgc tcatcatcac
62551  tggtcatcaa agaaatgcaa gtcaaaacca caatgagata ccatctcaag
62601  ccagttagaa tggcgatcat taaagagtca ggaaacaaca gatgctggag
62651  aggatgtgga gaaataggaa cacttttaca ctgttggtgg gagtataaat
62701  tagttcaacc attgtgcaag acagtgtggc aactcctcaa ggatctagaa
62751  ctagacatac catttgaccc agcaatccca ttactgggta tatacccaaa
62801  gtattataaa tcattctact ataaagacaa atgcacttgt atgtttattg
62851  cagcactttt cacagtagta aagattttgga accaacccaa atgcccatca
62901  atggtagact ggataaagaa aatgtggcac atatacacca aggaatacta
62951  tacagccata aaaaaggatg gttcatgtc ctttgcaggg acatggatga
63001  aactggaaac catcattctc agcaaagtaa ctcaagaaga gaaaaccaaa
63051  caccacatgt tttcactcat aagtgggagc tgaacaatga gaacacatgg
63101  acacagggag gggaacatca cacaccaggg cctgtcaggg gttagggggc
63151  tgggggaggg atagcattag gagaaatacc taatgtaaat gatgagctga
63201  tgggtgcaac aaaccaatat tgcacatgta tacctatgta acaaacctgc
63251  actttgtgca catgtacccc agaacttaaa gtataataaa aaagataaaa
63301  ttcagcctta aaaaaaagaa aaagaaaaag aaaagggtgt cctttcccca
63351  ttttatgttt ttgtttgctt tgtccaagat cagttgactg taagtacctt
63401  ggtttgtttc tggattctct attctgttcc attggtctat gtgcatattt
63451  ttataccagt accatgctgt cttggtgact atggccttgt agtttgaaat
63501  caggtaatgt gatgcctcca ggtttggttg ggtttttttg tttttgttgt
63551  tgttgttgtt tggttggttg ggtttttttgt tgttttgttt atttgtttgt
63601  ttgttttggc ttagtccttc tttggctatg tgggctcttt cctggttcca
63651  tgtgaatttt atcattgttt tttctaattc tgtgaagaat gatggtggta
63701  ttttgatgga aattgcattg aatttgtaga ttgcttttgg aagtatggtc
63751  atttttacaa tattgattct acctatccgt gagcattgga tatgtttcca
63801  tttgtttgtg tcatctatga tttctttcag cagtgttttg tagttttcca
63851  tgtagaggtc tttcacttcc ttggttaggt atattcctaa gttttgtgga
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64151  acagtttgac ttcctcttta atgagttgga tgccctttat ttcttcctct
64201  tgtctgattg ctctggcaag gacttccagt attatgatga agaggagtga
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64301  acttttcccc attcagtatt atgttggctg tgggtttgtc ataggtgact
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64451  gattttgttg aatgcttttt ctgcgtctat tgagatgatc atgtgatttt
64501  ggtttttaat tctgtttatg tggtgtatca catttattga cttgcatatg
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64751  tgaattgggg agggttcctt ctttatcttg tggaatagtg tcaataggac
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65301  ccttgaggtg tgaccttaga ttgtctgttt gtgctctttc agacttttttg
65351  atgtaggcat ttatggctat aaactttctt cttagcatcg cctttgctgt
65401  gtcccagaga tcttgatatg ttgtgtcatt gttgccattc aattcaaaga
65451  atttttttaat ttccatcttg atttcatttt tggcccaatg atcattcaag
```

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65601  taatttcaat tttcttaaat ttattgaggc tcattttgtg gcctgtcgta
65651  tggtctacct tggagaaagt tccatgcact gaatagaatg tatattctat
65701  ggttgttgga tggaatgttc tgtatatatc tgttaagtct atttgttcca
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65801  ctgtccagtg ctgtcagtgg agtattgaag tctcccacta ttattatgtt
65851  gccacctgtc tcatttctaa ggtctgttag taattgtttt ataaatttga
65901  tagttccagt gttcagtgca tatacgttta ggattgtgat gttttcctgt
65951  tggactaggc cttttatcat tatataatgc cctctttgtc tttttaaaat
66001  gctgttgctt taaagtttgt ttgtctaaga ataggtactc ccgtttgctt
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66101  tgtgagactc cttatgtgtt aggcgagtct cttgaagtca gcaggtagtt
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66201  atttaagcca tttacattca acgttagtat tgagatgtga ggtaccattc
66251  cattcattat gctatttgtt gcctgtatac cttggttttt tgtttttgt
66301  ttttgttttt taaattgtat ttttgtttta taggtcctgt gagatttatg
66351  ctttaaagag gttctgtttt gatgtgtttc caggatttgt ttcaagattt
66401  agagctcctt ttagcagttc ttgtagtggt ggcttggtag tggtgaattc
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66701  tacctgatga caatgtgcct aggtgatgat ctttttgcaa tgaatttccc
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66801  tggggaagtt ttcctctgtt attccctgaa atatgttttc caaactttta
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67601  gggtttctca gccgtggatg ctagcacagt atttagggtg tctcctaggt
67651  ccttcaggag caatctgctt cctgcagggg gtctgtgggt cctctctatt
67701  ttcgttttaa aggcagactt tgtaatagga cacactagtg ggcaatttat
67751  agttgtatac tcataagcaa actgtttaaa ttatctgaat ccaagtttcc
67801  tcatatgatc acaagatgag gtcccacaac aggtcgtctg caagctgagg
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67951  aacttagagt ccagtgttca aggacaggag gcatcccgga tgggagaaag
68001  atgtaggctg ggagactaag ccagtcttgg gaagtggctt aaattaggtg
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68551  accacttcaa atacatatca atttttgtgg tgtggctggg tgcagtgact
68601  cactcctata atcccagcat tttgggaggc caaggcaggg ggatcatttg
```

FIGURE 1W

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68651  aagtcaaaag ttcaaaacca gcctggccaa catggtgaaa ccctgtctct
68701  actagaaata caaaaattag ctgggtgtgg tggcggatgc ctgtaatccc
68751  agctactcaa gaggctgaaa caggagaatc acttgaacct gcgaggcagt
68801  ttgcggtaag ctgagaccgt gccactgcac tccagtctgg gtgacagagt
68851  gactcagtct cagaaaaaaa aaatgtggta agagaatttg aaatttagtc
68901  ttagtaattt tgaaatgcac aatacacatt actaactgta ttcaccacac
68951  tgtgcaatag atctcatata tatatatata tatatatata tatatatata
69001  tacacacaca catacacata ttgttcctgt ttaactgagg ctttgtgtcc
69051  tttgaccatc atctccccat tcccccaacc cccagcctct ggtaaccagc
69101  atactactct cttctaccat gggtttcatt gtttcagatt ccccatgtag
69151  tgaaaacatg cagtatttac ctttctgtgc ctggcttatt gcagatcatc
69201  tcattagatg cagaaacatc atttgatcaa attttatttc ataataaaaa
69251  tcctcaacaa attaggtaca gaaggaatgt acctcaacac aataaaaagc
69301  atatattata agccaataac taacattata ctccacagtg aaaaattgaa
69351  atcctttcct ctaagatcca gaacaaaata aggatgccca cttgagcaag
69401  atctagtgct gtgctggctt caggtctaac ccagtgcagt ctcagtgatg
69451  gtggccacaa ggctgcttgt gtcgcccctc accaagctcc aggcacctca
69501  gcacagagaa agagagactc gtttgtttgg gagaatgtaa ggaagagaac
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71551  agacataccc caagtcaata atagctggaa acgtcaacac ccaactttca
71601  gcattggaca gatcatccag acagaaaatc aacaaagaaa catcaaactt
71651  aatctgcaca atagaccaaa tggacctaat aaatatttat agaacatttc
71701  atccaacagc tgcagaatac tccacacact tctcctaaac acatggatta
71751  ttctcaagga tagatcagga taggccacat gttaggccac aaaacaagtc
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FIGURE 1X

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71801  ttaagacatt cagaaaattg aaataatatc aagtatcttc tctgaccaca
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71951  agagattaag aagcaaattg aaaaatgtct tgaaacaaat gataatggaa
72001  acacaaccta taacaaaacc aatgggatgc agcaaaagga gtactaaaag
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72601  aaaaggagag aagacccaaa taaataaaat cagagatgaa aaaggagaca
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74301  cacagaatgg gagaaaatat ttgcaaatta tccatctgac aagagattaa
74351  taaccagaat atataaggag ctctcatgac tgtataagaa aaaataaaat
74401  aatccaattt taaaacgggc aaaaaatcta aatagatatt tctcaaaaga
74451  tgacattaca aaccacaaac aggcatatga aaaggtgctc aatataatta
74501  atcatcagag atatgcaaat caaactgcaa tgagatatca tctcactcca
74551  gtaaatgaca ggcactaaca aatgctggca aggatttgga gacaggcaat
74601  aacaaatgct gacaaggatt tggagaaaag gacaggcaat aacaaattct
74651  ggcaaggatt tggagaaaaa ggaaccattg tacactgttg gtgggaatgt
74701  aaattagtat aatttagcca ctatggagaa gagcttggag gtttctcata
74751  aaactaaaaa tagagctacc atgtgatcca gcaatcccac tgctaggtat
74801  attcccaaaa gaaaggaaat cagtatatca aagagatatc tgcactctca
74851  tgtttattgc agcactatac acaatggcca agatttggaa gtaacccaag
74901  catccatcaa cagacagata aagaaaatgt ggcatatata cacaatggag
```

```
74951  tactattcag ccattaaaaa gaatgagaac ctgtcatttg cagcaacatg
75001  gatgcaagcg gagctcattt tgttgagtaa aataagccag gcacagaaag
75051  acaaacttca catggtctca tttatttgtg gaaactaaga attaacagtt
75101  aaggattaag aaaatgtggc acatatacac catggaatac tatgcagcca
75151  caaaacagga tgagttcatg tcctttgtag ggacatggat gaagctggaa
75201  accatcattc tcagcaaact atcgcaagga cagaaaatca aacaccacat
75251  gttctcactc ataggtggga attgaacaat gagaacactt ggacacagga
75301  tggggaacat cacatactgg ggcctgtcat ggggtggggg agaggggagg
75351  gatagcatta ggagaaatac ctaatgtaga tgatgagtta atgggtgcag
75401  cacaccaaca tggcacatgt atacatatat aacaaacctg cacattgtgc
75451  acatgtaccc tagaacttaa agtataataa ttaaaaaaaa ttaacagtta
75501  aactcacaaa gatagagagt agaatgacgg gtaccagagt atgagaaggg
75551  tagtggagag agtgagcaga gagggaagcg gagatggtta atggacacca
75601  aaaaaaacca gaaagagtga ataacgtcta gtatttgaaa gtacaaaagt
75651  gtgactatag tcagtaataa tttaattgta cattttaaaa taattaagag
75701  tataattgga ttatttgtaa cacaaaggat aaatgcttga ggtgatggat
75751  acctctttta ccctgatatc atcattacat atcgcatgca agtatcaaaa
75801  tatcccacat aactcataaa tatatataac tactgtgtac ccacaaaaat
75851  taaaaattat taataaatta ttagtttgat ttaaaaaaaa caaggatgct
75901  cacttttgcc acttctattc aatatagtag tggaagtcca tgccagagca
75951  gttagacaag agaaagaaat aaaaggcatc caaataagaa aggaagaaag
76001  gaaatttttg ctgtttgctg acaacataat cttatatata gaaaacccta
76051  aagattccag aaaaaaactg ctagaactaa taaattcagt acagttacag
76101  gagacacaat caacaccaca aaaatcacta gcatttctat acactaacaa
76151  caaacttttc aaaaaagaaa tcaagagagc aatcccattt acagtagcta
76201  caaaaattaa aatacttagg aataaattta accaaggagc tgaaagacct
76251  gtacacagta gtctataaaa tattaaaaaa ataaattgaa gaagtcacta
76301  atccttttta aatccaccat gccccagtcc agctgaacaa ctcatacttt
76351  tcagaatcta ctctatgtgt tctcactgtt ctgcagctag ccacctcttt
76401  ctcctcccta gatcaccttc tttatcattt ctgcttctca aaatgttacc
76451  cctctttcaa agcccaggta tgatgacatc tccctagtaa agctccctca
76501  acacctcaag cttataataa ctaatctctt ccttgaattc ccatagcagg
76551  ttatttgtac ctccattata atacctctct catcctgttt tgtattttaa
76601  ttattcatgt gtggcatgtt tctcttatta ggccataaat atcttaggac
76651  aagaactatg ccctcatttt tgttccacta caaatcttaa cacatacctt
76701  gcacacacca gaccttcagg aaatgcctgc taaggtaacg aagggacagc
76751  ctaaattaac ataaattatt atttgtgtac tgatccagtc ctaaatccat
76801  ggtgctatca tttctgtatc actgatggtt atccacttac ttaaataatc
76851  tttccttaaa tacacttaga aaagacggaa aactgtgtta taagggagga
76901  acaagtatgt aggttattcc tttccttaaa caaagagaag ttctgtcatg
76951  cgtcacggaa aattaaagca cagtaataaa aagcacgaac aagatttgtt
77001  gaataatgat ttagtggaaa cgttgcttgc ctcctgttca taggtcctaa
77051  ctttcctctc aagtacttaa gctgcacatt ctatttattt tgtttctagA
77101  TTACATTGAC AACTATTGGC TATGGAGACA AAACTCCCCT AACTTGGCTG
77151  GGAAGATTGC TTTCTGCAGG CTTTGCACTC CTTGGCATTT CTTTCTTTGC
77201  ACTTCCTGCC gtgagtatct ttgcaccaat aaagcagttt aaattagatc
77251  ttagagactt attagagtga gctctcacaa attcgtatgc ttgggaacat
77301  atctatatca tttacaaata taatttttcc gatataatgt tgacttttct
77351  aaatatatct acttggataa tttataaaat atggtcttcc cttggagaca
77401  cttaatctga gactttattt aatgtaggct catactttgt gaccaaataa
77451  tcattcagat ggctcacttt ttaggcaaca tgctactaag acatttaaaa
77501  tatttgcaaa gatttaaagc tatattcttt taaaactgat ccttccaatt
77551  tggtttataa tgtgtgctac ttaagagaca gatgtgcaca atggagtatt
77601  tttctcttca gatccatttg agtgaaaagc atatgacctt aaagggtgtt
77651  aaacatgtca gatgatttat tcattgtgtc atcatcattg attttttaa
77701  tgagcagttt ctgtatctta tcagaataaa gggcacattt atctgccccc
77751  aagcttctga ttatttttctc cttagtgaat gaagcctgcc tttctcatgc
77801  ttttattctc ttgtgtcttt aaaggcagct gttcaaaata ttacagtttg
77851  cccccatttc caagttcttg cttttgttcg ctccacctgg ggtagggaag
77901  gaggagccaa taaaaaggag ggttaacgcg gtgggagcag aagtgcttaa
77951  ggaaaataga tccagtcttg ctccagacac agctcaagct gtgccaacca
78001  gagaccccag agcacctctc caaagctctt ttaggtggta gggcttctcc
78051  tctgcctatt aataagtgca gagaacaccc ttgtcccacc agtgcccaac
```

Exon 6(E)

```
78101  ttgagattca ccagatcgtt ctgccccaga acactcaaaa tcacagaaaa
78151  gagactgaaa aggccatgca tatgcttggg tactagacct cagtttgaat
78201  acatctttgt cacatactaa ctatatgact gctttagttt actagggctg
78251  ccttaacaag taccacagac tgggtgactt aaacaataga aaggtattgt
78301  ctcacagttc ccaagactgg acgtccaaaa tcaaagcatt gagaaaccac
78351  gagagccatg agagaaagaa ctgttccagg cctctcttct tggcttatag
78401  atggctcttc ttcctgtgtc ttcacatcat ctgtgtccaa atttctactt
78451  cctagaagaa caccagtcat atttgattag ggtccatcct aatgacctcg
78501  ttttaacttg attacctctg taaggaccct attttcaaac aaggtcacat
78551  tctgaggtca tggggattag gacttcaaca tatgaatttt ggaaggacgc
78601  aattcagcct gaacagtgac cctgaataag tttcttttct aatagaatgg
78651  aggaagaatt attgagccca gagaaatttt gtgcggacca atgtaataat
78701  gtaagtcaag tgcttgtcat gaagagaact ctcaataaat gttacttccc
78751  tttgcctgta tgaatctaga aatacatgtt tcctggaaca aaacgatgaa
78801  atccaggaga attaaaaaaa aaaatcttac gtatccaagg caacttcatc
78851  tggcaatctc aacaattcag aacagagaag agattcactc aataatcaga
78901  ttccctacag gaaaatacct ttagaaacaa tacaacgcag tcttgggttt
78951  tttcccaaaa taatggcaca aaataattgc aacttttgtg tttatattta
79001  tcctgaggcc acatgtagag caacctctat gattcagtga aaaactatga
79051  acaaggaggt aggcaacctc tgggctgttg aaatagacaa caggctatgt
79101  tctgtcctca taggagagcc acttgagacc taattcataa cctagtcttc
79151  attcagagaa aattctgata aactcaccta tatggtttca caattctttg
79201  aagattataa acaataaata tagaggaaga tgatagaaca aacactgcaa
79251  cagaaagaaa tggtaaaaga ctaacagcaa agaagggaaa aggaaatctg
79301  tgagtagcaa gcagacatca atgttcaaaa tgtgtatcct gtcagtaaaa
79351  ataaaattaa attaaaaggg aaaacaaaat gtatgaagat ctagggccaa
79401  ttagtgttag ggtcaacaaa cctctggaag ttggctgcac ccagcacagc
79451  aaaaaggcag tccccataat gaaactctaa actatcacag ggaggttaaa
79501  tatgtcacta ggttaagtta aaggtcagag actaagtagt cattcttgga
79551  aatgtttcca ataaagtaag tatgaaattt ttatatgcaa attaaattaa
79601  cctatgttgg aaatctgaaa attttgcttt cacagaaaat tacatttctt
79651  aagaacccca agaaaagtaa cctctactaa ggatctttta ctgaaacttc
79701  acaatatttt ctgagtcctt atttattaaa tgaaagactg aatggtccat
79751  atataccttt agaaaaaaac aagattgcca gagattttat tatatcctgt
79801  gtatctgcca accaaaagag ttgtctgatt gaaatttagg aagacacatt
79851  gacattttgc tgagaaagct agaggtggat tgtgggctgc ccctatgtag
79901  ggttcctccc acccaggaca cctgagaacc aagaaagaaa agagcctttc
79951  tccatcttac cctcaaagca gaagggccat cctgcacatc acagagtcat
80001  acaagccacc catccaaagc gccactgtgg ggtcacttcc cctggtgccc
80051  gctccatctc tgggctaatg agctcacaga agaagcccca gctcccctgt
80101  gttaccctga tatgcaggtc tttctccttt ttagagtgct cccttgtctt
80151  ctgctagata ttcctgctaa gagtattttc attgatgaag aaattgagtt
80201  ttatagagac tgaattcctt gagacctcca gctagtaaat tcagtgcaag
80251  aactagtgct gtttgactca agatattaac cattccatta aaaatattgg
80301  ccactgtaat ccttaacaat attaactaaa tgtaattatt gcatataata
80351  acatgttaaa aaccgtttaa aaaaacaggg catcttgctg ggcgtggtga
80401  ttcacgcctg taatcccagc actttgggaa gccgaggcgg tcggatcaca
80451  aggtgaggag atcgagacca tcctgcctaa catggtgaaa ccatgtatct
80501  actaaaaaat acaaaaaatc agccaggcat ggtggcgggc acctgtaatc
80551  ccagctactc gggaggctga ggcaggagaa tgatgtaaac ccaggaggcg
80601  gaacttgcag tgagccgaga tcgctccact gcactccagc ctgggcaaca
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80701  tttcagcatt gcctatttgc tatgtgtggg ttacaaatta ggttcattta
80751  atccagaaga taatgaaggg taaatttctt tacatttatt ggtgtcagta
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80851  tatatacaaa tataatagac cttattttca cagacttctg tttaggtgca
80901  ccaagctgtg tactaagaga gaggtggaaa aaaattggaa aggagccatg
80951  atgagacaat aagcagacct ggtttaataa ctgctgtaat gtacagtctg
81001  gcgcaagaaa tacgtagtga acatttacca ttcactaata tatgttaccg
81051  agcaatgcca atgtgatttt cagcacattt tagattgttt ggcagatgat
81101  aaatttgtgc tatgtagggc ctgtctttat tttccaaagg ggattaaact
81151  ccgaacctca catccacatc ataagtgctc aaaatggtag ctagtgctgt
81201  taattcaatg tctgcaaaat ctaaattatg ctccatacaa gtggattata
```

```
81251  cacatatatg cacataaatg catgtatata tactacatat tataaatata
81301  tgccagaaat tttggtattt catattctct tacatgtcta cactttatga
81351  aaagtagtat taaagggaaa ataaagaaat ctttcctaaa tgatcttaca
81401  cagcagaaaa aaattagaag ttacaaatga cttaagttgt tctggattta
81451  gaaatggagg ggcattttta taacacctaa atggagggaa atgttgttta
81501  aatctataaa ccagatcaca gagaccaggt ttttataaag cttagtttgt
81551  acaatcacaa cctgtatgag atagagatct tagacagcgt aagacagtca
81601  ctgaaaagga gagatggaaa acagaacctc tgatgtaatt tctaatttca
81651  tagtacagtc atttatacta attaataatg gagtagatca ttgctcacga
81701  gtagcaaata gtattatcag accactgcat attttaaaca tgattgcatt
81751  acttattgtc tggttattgt cactgatgta ctcagaagtg tggaatctca
81801  agataagaag gaaggttaaa ggttatctag agcccaaaaa tatctcagcc
81851  aagttgttat tcagttgaga cttaacacct tctagaaatg aaaaacccac
81901  cacctctcca gacagcctat agcatctttg aaccatcttt gagctactct
81951  aaaaataaaa agaaaagaaa agcaaccatt ccttacctgt agcaaatact
82001  gacttagtgc ttataaaatg tccatctcta acgaaagggt tagactcctt
82051  gaagtttaat aaaaaactaa taatttatag ctagcaagta aaatccacag
82101  acttgaaagc agcagagctc ccagccccat gctaataaac tcaagagtta
82151  aagacaaagc ccagagactg aatttagcaa gctccaaaag ccaacccaag
82201  gctgagacaa agcatcttgt ttttacaaat gttagtagac cagagcaaat
82251  tgaaaagagt gggggacatc aaagaaccag aattttggca gatcaagatg
82301  ataagcagaa gaaaagcaaa ctggcccaaa actaatgtaa acctagaagg
82351  gaatactaat cttactaatc ccaaaaactg aataggtgag ccaaaataaa
82401  aaaggcaagg aatggtaaaa gtgtgaatta aaatgggaat gtgctttgca
82451  atgatccacg ttcttgtctc tagtgtacaa atgggcaaaa tagaaaacct
82501  tctactctgt atcttcaaaa ctgagtatcc ctgctctcca ttttacttct
82551  cttttagtag gtgtacagtt ataacattat aaagaactac agctgggaca
82601  gattttatac agtcctctct cctccatttc atgaatagag aatctaactt
82651  tcagagtctc atcaaagtgc tagaagtatt cccatgttca cagcagtgag
82701  actttaactc cctcagattt aaaatccagc tctgtcccaa gttgaaattc
82751  atgttctcta cattccatca ctggatgaga ccattcaatc taacttaggc
82801  aaaaagaaat gtcacagaga aggccacaca cacaaaaaaa aattttattg
82851  tgattttatt tataatcatg gtgcctatgc tataccacaa aagataataa
82901  atgacaatgc ctaattgact tactaaagaa cagaagttgt atctcctggc
82951  agtattgccc aacaatttgc cattggctat tggtattata atggagataa
83001  atactgctta ttttaataag taacatgttt atggacaggt tacataccgt
83051  ttgtcttctc tcagactcat tttagtgact ttttaatatt tgtattattt
83101  aacagtgctt ttgaaatttt tgagtgccat ttttgtattt tgttccagGG
83151  CATTCTTGGC TCAGGTTTTG CATTAAAAGT ACAAGAACAA CACCGCCAGA   Exon 7(C)
83201  AACACTTTGA GAAAAGAAGG AACCCAGCTG CCAACCTCAT TCAGgtaaat
83251  gtcaatgtaa taggtagatg gcaacatttg tgtccatagt gcttgatggg
83301  tcattttcca atctctgtgc ttcattgctt ggtagaacta ctgctttgtt
83351  ccttttcata aaatgaagtc agaacttaat gtacagtctt ggatttggac
83401  agtcttggat ttgttcctcc tctcccaaac tgaaacacat gtatttttag
83451  caaatggtcc atgcattgtt cagactaagt aaccatgtca gcaaggccat
83501  gcaaaggtta gcagttgtgt ggctcgtgga attatctaat atgtcttatg
83551  aattacttga tgaaacgtaa ttgatcatta agtgatggag cagaacaggg
83601  cattgttccc tgcattccaa ttactttctc cagccagatg tatgttgctg
83651  ttttaaagaa caacatattt gtttagaatg tcaaggttta atacctgtga
83701  aattgctttt agtgccatct agggcagtta gcggaaatag ctatcctatt
83751  ttgagagctg atgggactat ggaatacatc agtgtttgag aatattaaac
83801  aataagtata taatttgaag ctagctccta atacataggt tgttatttag
83851  tatttcattt tcttttcact aactcaggat tagcttcagc actaaaagga
83901  atgcttctcc ttttgccatc catatatttt ccatcctaga tccaggttaa
83951  gaatcacaaa atatattttt tgttagattc ataatgtaga gttgacattt
84001  agttatggac aaaataattc tacaatctaa agtttctccc ctcctgctag
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84101  ccaaggccct aggaaacttg ccttaaagct gcagtaacgg gcacactgtt
84151  ttgttgctgt tgttgttttg ttttattttt tgtttgtttt gttttttttt
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84251  atctcggctc actgcaagct ccgcctcccg ggttcacgcc attctcctgc
84301  ctcagcctcc cgagtagctg ggactacagg cacccgccac cgcgcccggc
84351  taatttttg tatttttagt agagacaggg tttcaccgtg ttagccagga
```

FIGURE 1AB

```
84401  tggtctccat ctctcaacct cgtgatccgc ccacctcggt ctcccaaagt
84451  gctgggatta caggcatgag ccacggctcc cggccacaag cacactgttt
84501  taatttagat tgtaggtttg ggtgggtggg ttggtgggag ataaccacca
84551  caacccctac ctttagtgtt gatctgtgac tgtgatatat gcagtgcctc
84601  ccacagacat ggagctgggg aaagaagggg gcagtatggt tcagttatat
84651  catgaaggag atctgtttat atctaatcat taaatgagga tattaatttt
84701  taaatcaagc tattcttcaa ctgttgacaa gaaagtagac catcaggcat
84751  gacttccagt gcaaatcact gagaatctct atttttttac attatttttt
84801  acaatttttt ttttttacat attctttaca ggtttttaaaa ggtcactaaa
84851  gagaaagtaa actctatttt cttatatgaa gttggagttt aagatctgat
84901  gccaaacaat aatcagcaga atgaaaagag gagtcacaca ctttaggaca
84951  cacgcaaaat accccaaggt ccagaattca taggctttca tcctttagca
85001  ctccttaact ggttacacat gttccaatac ttctaataag tttttctctt
85051  tactgttctt atcctttaat tttccttcac tctagaacaa cgttttccaa
85101  cctgtgagtg cagaagttat tgcatgggtt cctttcatcc gtctgagcac
85151  caagctctgt ctacatatgg aaccaataat acattttaca caataaaacc
85201  tcttggaata tcagctgttt tgttagaaag tgagctcttt gaggaatttc
85251  tcatgcacat atcaattgtg atgatacaaa gctgtgccgc tcaatacagt
85301  aaccactagc tacatgtagc tttttacatt taaattaatt aaaattaaaa
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85401  ggtggctatc ggctgccata ccatacaaga gaaatataga gaataactgc
85451  aggaaatctc ctgatctaac ttgtcattat tgactactaa actgtgcaac
85501  aataatttcc aattgaactt gaaaataaat tgttatttct acagcaaatc
85551  attggagcag aggcatttat atgtctacag tcaaaatgag gcaaggcctc
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85651  aggcctagaa ttttatttta tggaactggg ttatgtaaca tatattgtga
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85751  gtttttattt tacttaaaac tccaacttaa atgttgttct taacaaaaat
85801  aatgcaaaat ggaatgcttg aagcattcaa gagtactttt aaaatctaat
85851  catagtttca ttaatcaaag tagaatctac taattttaaa agcaagtgct
85901  ccttcattta aatgcaatta atttattaca catagaaata ataatataat
85951  tattaatttg ttcattgttc ttccttgcta tagtctttag acagaattca
86001  aggctttaag ccttgattat atattataga aatttatatt tcaggatgta
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86251  catttcaggg ttttaggaaa aaaatttaaa accccagaag cttgcagcaa
86301  atttagctgt gtcaatatct ttgcatgatt cttttaaatt tgcttttcat
86351  ttcaagctgg agcagtctgg aaaaagaaat tagctctcag taatgttttg
86401  aatacctgcc caaatgtcac aacttttatt aataatgctt aagactcatg
86451  aagtgctttt tagtttgcag ggtgcttcta atacattatg ttacttgatc
86501  ctcgagacaa gcctaggagg agctaggact caaatccctg ctgtctgaat
86551  ctgaatccat tacccctttc aaaaagcagc atttacatcc tcataaatat
86601  atgctttatt agaaacagaa acagggaatt aagtaaaagt ttgtgaaata
86651  aatgttggta gggatagatt agaagatgtt gctttgatgc caactgaccc
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87051  aaggtaagat aaagttgtga aaatttccct gaaactagaa taaacagaga
87101  ttgaaaataa agcaaaaaag ataagaaaca tgaagtgtcc atccaggcat
87151  tccaatatcc agctaataaa gatgtctcag ctcaagtgca gggaaactaa
87201  gaggaagatt ttatcaaaga aatacaacat tatgattctc cagaacagga
87251  ggacaggagt ggccacagta gaagagctca ccaagtgtcc agcactgtga
87301  accaaaaact tcacaccaag attatcacag taaaatatca gaaaacttac
87351  caaaagggga tcctaaatgc tttctgagca ggacagagcc aaaggaacaa
87401  gaataaggat gacataggat ttctcattag taatccaaaa attagaagac
87451  aatgaaacaa tactttcgaa attatagaaa ttattttcaa cctagaacgc
87501  tatatccagc caaaccacca tcaagtgtga gagcagcacc aaggcacttt
```

FIGURE 1AC

```
87551  taggcatgca agatctcaaa aattaatcta ccatttacct ttactcaaga
87601  aactttgtaa atagaacttc tcttccacaa caaggggata agccaagaga
87651  gaaagagaca tggagtcaag aaaacaagag attccgcaca ggaaagagca
87701  aaggggattt ctatgataat agggaaggga agtcccaaga caacagctat
87751  gcaggccttg agaacagaat gagaaggagg ctgagagctc caggagaaag
87801  atcttcaagg aagcgaaaga atggagttct cagatttcat gatgcatttg
87851  accagaggaa ttttatagtt ctgttggaaa gatctggaat gtaatcataa
87901  caggtacata taggcaaatc aagaaattaa aatagggcaa ttataactcc
87951  aaaaaaacca aaaacttgta taagaaagaa agagcagcca tagtacatca
88001  cattgctgaa ctgggaacag cagttacatt gtcataataa tattaaatag
88051  taacttagct aagaattgtg atattaaaat gttgatagga tgaaaggagg
88101  ggaagagggc atgtaagtgg gcaatatcat tatcgttcag gataggaagt
88151  taattgataa tgtctaaaat tgaaaaatca agaaatataa ctataagcat
88201  aatccttaaa aataagcatt cttggctgga cgcaagtggc tcatgcctgt
88251  aacccccgca ctttgagagg ctaaggtggg aggatcactt gaggccagga
88301  gttcaagacc aacctgtgca acatagcgag accccacctc tacaaaaaaa
88351  ttttaaaaag tcaagtgcaa tggcacacac ctgtagtcct cacacacctg
88401  tagctactca ggaggctgaa gccagaggat tggttgagcc tgggagtttg
88451  aagctgctgt gagctataat tgtaccactg cactccagcc tgggtgatag
88501  agtatgaccc tgtctcaaaa ataataataa taataaataa ggattcttaa
88551  aaatagaagc aacaactata agaattgaag gggttgcctc tgaggaacag
88601  aaagtagtgt gaagaaagat gtggaaaggg attgctggtt catagcctaa
88651  aactttcagg actttcacat tttaaactct gtaccttgaa aaaataagct
88701  ctgtgttcat tattcctttg gatggtcagc tgaaacgttc taaaccattt
88751  ccagtaagga tcaaacatgc cataatggta atacttgcaa gacaaacaaa
88801  atactcccaa aaaaactgaa ttatactggc cttgtactta ttgagcaaag
88851  tccaaatctc tttgactgcc tagagcacca gcatcacctg ataaatggca
88901  aagttggctc tcattttgct tcttgttgat ttgtcctttg aattgtatac
88951  accatgtaaa ttaaccatag gaaatccctc taagtgttat ttttctcttg
89001  ccaactactg tgtgattttg gctttaaata taggaacatc agctactgga
89051  tcacagggat gtgggttcaa agttcagcta ctagaaacaa tttgctaaga
89101  gagacctaag aacaaaataa agttattaga gtgtaacggg catagagttc
89151  cactttccac cttcattttt actgttaact aatatcagcc atgtgacaga
89201  tgccacctgc accttccata cctctcattt aaaaggcatt tttgggagat
89251  gagtaatgaa gggaacaaga gcttagctgt tgggatcaat ctgagagaaa
89301  aatagcaaga catcaggtct cattgtaaag aaaatcttta attttctcag
89351  agtggcctct tttgccccca gttctttata acattcacag gcaatgcctt
89401  ggtcccattc ttttgttgtt ctgttgtttt ggatttttte actggtatct
89451  aataatgtgc agacctgcca tatgcttcta gttctacagg agtcttgctt
89501  tcaatgtatc aaaaatcata tatgtgtgac atcttctatg gaaattgttt
89551  aattaaggca gccgtctgtg tcatcacaac attagaggat ctctgggcat
89601  cactactaca gaagaagctg caatcctaaa tccatgtgtt ttccttaatt
89651  attctaaatc actctataaa ttgtgcaggt ataatatttg caaagattaa
89701  catttcaaga tgatgcaaca atagttgcat tatataagat gtcaagatac
89751  ttagcacaaa tttccacaga tttgtagatt aaatcagcat gagccatgta
89801  atgaaggcaa ggaactttgg ttcaatcatt taaaccttcc tcaaaaatat
89851  aaaaagtccc tcagtttcta ccactatatt tttctagttt ttttatgtca
89901  ctttctgaaa tttcattgaa gtacaatgtg catgcagaaa agagcacata
89951  tcttaggaga actgagcaca cctgcataac cagcactcag ataaacagag
90001  caggacctcc tgtgtacccc ttcgcaatca ctatcccata aggataacca
90051  ctgtgctacc ttctaacagc gtagaatagt tttccctggt ttttgtacat
90101  tatggaaatg tactccttgg tgtcttcttt ttctcactca acgttattca
90151  catgaagttc atccatgttg ttgtgtgtag ctatatgtac tattgccata
90201  tagtattgta ctatgtaaat ggtgtcacaa attttctgtt tattctactg
90251  tttctgggta ttttggaatt tccagcttta gtttattaga aaccaacata
90301  tagtacatat cttttaatga acatatataa gcatatattt tgaaaatata
90351  cctaggagtg tgtagttgta tcataggata cttaaatgtt cagctttcgt
90401  agaaacttcc agttttccca agtagttgtg tgaattttta acttttattt
90451  agcatacatt tattcaatga tattctcagg aaaaggaata ttgttagatc
90501  acattttctt cattatggat ttcacaatca tgactgatgt gttatgtact
90551  agggatgtgg cccatttaaa tgaattggtc tgccaggcat ggtggctcat
90601  gcctgtaatc ccagcacttt gggaggccga ggtggcagat cacctgaggt
90651  gaggagttca agatcagcct ggccaacata gtgaaaccct gtctctacta
```

FIGURE 1AD

```
90701  aaaatacaaa aattagctgg atgtggtggt gcgtgtctgt agtcccagct
90751  actcaggagg ctgaggcacg agcatcgctt gaacccagaa ggcagaggtg
90801  gcagacagcc aagattgtgc cactgcactc cagcctgggg gacagaggga
90851  gaccctgtct caaataaata aataataaat aaataggttt gtcacataaa
90901  ataaaatgtt ttgattaatc tactataata aaaaagtttt ctctgagggg
90951  actggagtaa atacctggcc attagagatg tttgcagact cattaaaaag
91001  aaagaaattt accaaaatct atatgggaaa gtaaggtcgg gcaatctctc
91051  aaatgagcag ttcagatgga agcttttcca ataacagtct tcaagcagtc
91101  agcaagtctc cgtggaggga ttctatgact gacagccagg caatctgaga
91151  tattgtctca actccaccaa ctttgtataa acctcttcat ttatctgagc
91201  ccttttttc tcacctacaa aaaaggaatc ttaattcaca ctttgatggt
91251  gaggatcaca taaaaatact ttgtcttatg tatgccaggt gtaattatat
91301  gaaatggaga gagttgatgt tttacatcaa agagctataa acatattctt
91351  agatcatggc ataaatccgt aggtgttttg cagctataca cctagagagt
91401  acattttccc catcttgttt tagttctgct tcttgatatc actatcttca
91451  tttttagcat tagaagtatt acatagttca aggatttcat taattcaatc
91501  actagcatac cctggtgttc attagttaac tagttagctt actagttgca
91551  taatggattt tcattagtcc tttgcttctc ccttatcaaa tattgattaa
91601  agatcaatct ctagaatgta tgctcatgct caagtcgctc acctaactac
91651  tatcttggat attagcattt aaccagtcaa tcattacttt ttgttttgga
91701  taatatagta tctttccctt accaattcaa aaattacatt atattgcact
91751  ttttgggcct tttgcttctt ggtatgttgt tttgaaaaga agctctggcc
91801  aggcacagtg gttcatacct gtaatcccag cactttggga ggccaaggca
91851  ggcggatcac ttgaggtcag gaatttgaga ccagcctggc cagcatggtg
91901  aaactccatc tctactaaaa gtacaaaaaa aaaaaaaaat agccaggcat
91951  ggtggtgggc acctgtagtc ccagctactc tagaggctga ggcacaagaa
92001  tcacttgaac ccagaaggca gagattgcaa tgagctgaga tcgcaccact
92051  gcactccagc ctgggcaaca gagtgagagt ccatctcaaa ataaataaat
92101  aataaaataa aataaaataa aagaagttct gatgtggtgc aatatgttta
92151  acagccagct gaaaatgcca aagtagcctt cttcctcctt tgggtattta
92201  tcagggctaa gtataagagg caaaagattc ttcatgtgta gtaacttaat
92251  catttctctt tttattttat tctaaatcct gctctctttt ttctttttca
92301  tgtccccatc tatgccacat gcagTGTGTT TGGCGTAGTT ACGCAGCTGA
92351  TGAGAAATCT GTTTCCATTG CAACCTGGAA GCCACACTTG AAGGCCTTGC
92401  ACACCTGCAG CCCTACCAAg taggtatcag tgtgacagct gccactgtag
92451  ttgagtcttt tcaagtctgt taaacaaacc atacccacac acacaaaaaa
92501  aggtgttaat gtttggcttc tcttattctc tgttgctcct agagagattc
92551  aaacctattt agtagcagtt ctggcacaaa actaaatgga atcagtatca
92601  ttcctcacaa tccacagact ggggttaaag attaaaataa tgtaaatttt
92651  atagagattt atttttacta tttcatgctt actttctaat gtctcatttc
92701  gtaaagccca ccagcatcct aaaggtaagc accacagttc ttgaaaaaca
92751  aggattattt attttgcacc catcgcctga ccccaagaga tgagtgctta
92801  gagagtaatc catctttgta cgtttagatc tctcaaagcc atttctcatc
92851  tggatcctct ctggatggtc ctcaagcttt tacttgcaga tcaaactcac
92901  atcagtggca aaaaaagaga aaaataggag tcctaatagg attatagttt
92951  acaatgaggc aatgggaccc agcggattaa aatttggaat ttgcattcac
93001  aattttaaag taagactact tttcttcaca tttcattggc caaagtaaat
93051  cactcagcca tgcctaaatt caaagaaaat ggggaagtac aattttacct
93101  tttaccatgt gcctagaagc aggcaagaac caaggacatt atggacagtc
93151  ctaatgatta ccacagagat ctgtaattaa aaaaaaaaaa aagggcttag
93201  tcttggagtc ttggaaacct ggactccagt tcaactatca cagaaaatgt
93251  taaatcatat tcaccaccta attaaagaag tcctcattga aataccgaag
93301  cagtaagtca tgagaaaggc tttctgtgag tcacccagct tgattagcgt
93351  agtcagttcc tcaggttgtt caaaagttat taaattgctc atccgacatt
93401  tgagagcacc agctgctttt cttcatagcc caacaaaacc ttaatcctag
93451  tggcttcatg ggattcggga cacctaacta ctgtgactca caaaaaacca
93501  cctgttcgta ctgatcttgg gagatatcag ctgaggaaac ctccatgaca
93551  ttccctggca gtaccgtctt aatggaggtt tgtgatgcag cagaatgcat
93601  accattggga agcaccagat ccatcattaa ctacattact tccctgttct
93651  gcccttggcc tcagttttcc cacccacaaa gagaaggaca agagttgggc
93701  aagatgattc ctaagctcta atgggaaatg cctcctggtg ggtggtatct
93751  aaaattcttg tcagcaccta ggacagagat attcatagca ctccagggat
93801  ttcagagagg atggaacctt agcatggata gaagcatgga tgctgttgaa
```

Exon 8

FIGURE 1AE

```
93851  tgcatgtttg gattaaaatc ctcttttcat ttagatcttg aagtttagtt
93901  gaacttttta tggagtttaa gacccttca acattttgat atcaaaaaac
93951  cgaaaataga acctaactcc tgtgccattt attccttggg agtatgaacc
94001  aaaaataaaa attatataga aattgtattt cttgtcttca tgaagtttgc
94051  taggtaaatg taaaaaggga atctgagtag gaaaactgat agagaattct
94101  caagtgacag aggagagtgg tctattatca tatgtgatta tttggcttcc
94151  cacttactgc agtttttgga ttaaaagtca ttaaaagcct ggaaaaactg
94201  tttaataatg agtcaaattc ccccagtaaa tcaactatta ttttattcac
94251  ataagttctt tctactcctc tgatattttc cctgtcttaa gtgggggtgg
94301  aggtggagga ggatttatgc aaacacctgt gttcctcatg tcctactgtg
94351  cctttccctc actttccttt tcctgcaaac tcatgaacca tggggctcag
94401  ctccattgaa tgaagaacag ttatttgtcc agaatgacac agcagtcact
94451  ggtaaagttc atgggaaact agatgtccta acatctctcc ccttccagtg
94501  atgcttcatt gcttcaaaat gcagaggttc ttaatccttg ttgatgtttt
94551  ttgttaaacc attgagaatg tgatggaaat tatggggtct ttcccaagaa
94601  agataatcaa tgcacgagaa aatcaatact ttgcctacaa ttttaatgta
94651  ttcacagagt ccctgaagcc aagttcaaac ttttgtttta caaagcaaac
94701  ttgctttaat caagtgacaa taattttcag tgacttagag ggatcttttt
94751  acatttaagt ggcttaccga atggagagtg ttgtagtaag aaacagacta
94801  caattactat tttatttaca ttgtgtattt tcctttagca ttcagcctaa
94851  gaacttctga tgggaaagat catttattca gtcatgtatg cattcaacaa
94901  ttactcattg agcacctatg atgtgcaagg catagttcta ggcactgaga
94951  atgaagcagt tggagtaaaa aaaaaaaaaa agttagaatc tctggccttg
95001  ggaagtatgt attcaaggga tgttgggata gacaatataa ataaataaat
95051  ataggatatg ttagatggca ttaagtgcta aggagaaaag taaaataaag
95101  aaggaattta gggagcatca gaggctataa tttcaaatag gtggccaggg
95151  ggaagatcaa tttatcaaca atatcatcat catcatcatc aatgttactg
95201  ttatcattaa aaaacaccag ccccatgctc ttgttcccca gttttaaaga
95251  catagtggga tgctttgatt ccactaaaca ggatgaaaga gaggtctaag
95301  aaacagctgt gcagggcaga gagaaatggg aggagggaca ctcaaacctg
95351  ccagggatac aaccagcagt tccttactct ctcttttcag gtctggtttg
95401  tctcttacat acactctaga ggtcttagca attctatttc aaagttttat
95451  tttaataaca gaaggatgta tagaagcaag tacttttctt gattttctcc
95501  tcaaagagag tgaagctgca aagggcaaaa cacaggtaaa tatgctattt
95551  agggaatgag tcagaaattt tatgaggcta tggggaatta tcaagctcca
95601  aaaacacctt gtggtacctt aagaagtggg gatttggaga ttatctaacc
95651  taaagccttt gatttactca taagaaaacc aaaacctgca agcaaataag
95701  gtgcctgccc aaaggcacac agctcgtttg caaagagtac agaccctaca
95751  ccatggtgct tagacctaca tttgctaaaa tgagttatta caaatgccac
95801  ccaacagtat aggctaaaag agttttggta aatattctat gtaccttatt
95851  tactccaagg aaatttagat tttatacgat acaaaaaaaa atctgcctca
95901  gcaagtgact gagatacaat tcattaatga atccaggttt agaaaccaaa
95951  gtctgccaga tgcacagaga acagttatgt tgtaactagc aacattctaa
96001  gagcccttgc taattctggt tagatcagaa ccacttttc ttagccatgg
96051  atagctttgg ctaatgaaaa gtctattgtt ttttattcta tgtgggcagt
96101  cttggctttg ccaagtaaat gttgtgctat ctctggtctg tatcacaaag
96151  aatatatgtt agcaagttga gtacatttat tataaagaac actgcttttg
96201  tggatcttgc atgaaaagag ttacttaagg tatttgattc cccaatctcc
96251  aatttggcca ttatcaagtg ctataaatat attcactggt ttatcatcat
96301  ttctcttctg cctgcacgca cctgaagGAA AGAACAAGGG GAAGCATCAA
96351  GCAGgtttgt gatttctctc ttgctacatg tttgtttata aatctgatac
96401  ctaccaggtg ttttaaatgt gtctcatgtg agtaaaatcg atcaacaaat
96451  acaagatgat taaaagtgac ctttcacaag attgcctgca aagattgcta
96501  ttttattgat atttcgcccc ttagtatcaa agtgtctttc cctaactcac
96551  tccctgcttt ttcaaaatct gcagggcatg gaacatttgg aggtgggga
96601  ggaggggaac tgatcttgga ttagtccttg ctgttgtttt cccagacaga
96651  agtcttatca aagtattcaa atatggtaat ctagagaatg aaagaaagaa
96701  attttttttc tgaatgtaaa aagtccaggc agcagtctag gatacactcc
96751  ccttcactag ggtccttctt ttggagtgat atatatatat atatatatat
96801  atatatatat atatatatat atatatatat atacacacat atatatatca
96851  tatacatata cacatacata cattatatgt atatgtatat atacctatac
96901  atataatctt tttttttgg caagatgaaa ccacctctct gtgacatctc
96951  cagatctcca gcccactgag tgctgaggtc tactcaagtg actcaaagag
```

Exon 9

FIGURE 1AF

```
 97001  ccccatcccc atcttttagg aagaagacaa ccctcccaaa aattccccaa
 97051  ataatttatt atcagcttcc catgacttag atggaatgcg tcgtcagatt
 97101  acagcagaga attaaaccta gagggaatac gaggtgaaag aaaaatttct
 97151  tgatctgtgt taatgagtac caggaagtgc ctagatttga gagcaaagcc
 97201  ctgaaaaaca gagccaggtg gaacccagta ttaatgatgt gaagagtggc
 97251  agaggcagaa ccagcaagga gaatcccagg tgcctggaaa ggaagaagag
 97301  atacattttt tttcctatca ttgtcactgt gtttccataa agaaatgaag
 97351  gcatccacct acccagagtt ggtccctaag tggaggccag tgtgggccca
 97401  gggattgttc ttttagctta gtactattat aataattata ttaataataa
 97451  tatatttatg caatactgaa gccagttttg aaagttcact tggtgtatta
 97501  aggctctgga ttatccattt ttgcattatg tttatatgta aagataaaca
 97551  aatgaaaaca taaatgcatt cgtctatgat gggagatagg cacgatagga
 97601  tatacaacat caggcacatc ttctgcgtag gtaacctacc caagggatgg
 97651  cattaaagtt ctttctctta tttggtagca tagagttaga gccaagggca
 97701  ttggatattc cttggagata tttccagaaa aaagtcattc ttccccacct
 97751  aagaaacgtt tttgaccaaa gagaggttct agtcattaga ttcggaatag
 97801  tctttgccta gacactggaa gagacaagct gaccaattct agacttttag
 97851  tccatttttct agattccata cagagctcac catccttctg ttgtgacaat
 97901  tttacttgaa aaaagttaca caaaataaat catagccatt ttaaggtagc
 97951  ttatagttgc tttggtgata ttttaaaagc tttcattgtc tcaggagctt
 98001  tccatttact aattatctca aagggtgatc tgcctccaaa tccaaaggac
 98051  agagaccatc tttggcacaa attccagagc tacctgagag tgcgatcacc
 98101  catcttagtt tcatcctcca aaacggagct gttaacacct aaaagagaag
 98151  tttgtaaatg acatggaggt gcttgaataa gtgtaaactc tatggcaatc
 98201  ctgaaggagg ggacaccttg ggctggcaca atgatattgt actgttttta
 98251  aatgttagca cagcagaaaa caaagacaaa attaaagtgt cactgttgag
 98301  cttctgctca ctagtccaaa aacaagcttc ctattcagtt atcactattc
 98351  aaaaaaacta ccaaccaaat tttccacatt tatgatgttc gcatatatct
 98401  acgacattta cctctctgca tgcagcagac tgaggttgtc aaagataact
 98451  cacccatagg tttaaatatg tacaaaacca ctgaagtggg ttgatgactt
 98501  agagaatcac acatggaaat ttcttgcttc tctgtggtca ttgaacattt
 98551  ggcaaaaacc accttgaaat aagtcctgca ctattactta gcctagattc
 98601  attatttaat atcttatatt tcatacactt aggtgtccta tcttccaact
 98651  agctgtcaca tcaccctggg taaagctatt acagaatgtg ctcaataaat
 98701  aattcttgga tagagtaata aaatggccct gacctcaagt agtttgtggg
 98751  aagagataaa acaccaacaa aaaatgggaa gagaggagaa atataaaaag
 98801  agaaataaaa aattaaaaac attgcaataa tctaaggaaa gtaagctgaa
 98851  gctcccattt aatattatgt aagctttcac cttgttgtgc tccatacaca
 98901  gaatttataa tcctgcataa tgaatgcaga aaggctattg taataacaat
 98951  agcaacagta ccatcttaga aagtaacaaa gttgtcctta cccaagcaaa
 99001  atatcacaaa gtaaaatgca tttataatga gagttcttcc ttacagaaga
 99051  gtagatctgg gtccagagta ttgttaatta atgcttgacc ccatttcaaa
 99101  ggaactaatt aacaccaccc aactgcagag taatttactg cctttgggac
 99151  cactgagtta ttgatggtga gtcagaaagg cagaggagac aagcttcagc
 99201  ccaagcagga gccaacattt tcacctttta gcccagagct tggaatctcc
 99251  taagtccttc ttcatggttt ttctttgtgt tacaaactga gagaaaccca
 99301  agtgtagatg aactcaacac agcagccaac atccgcctct gggtgcctgg
 99351  cactctcacc aaaggacgga gccatgactg tagagtgggt catacacaga
 99401  gaggcttttc tttctgcaac attgattaag atgtcgaaca catttataga
 99451  acccttagtt aactacattc ccggctttgg aatgttcttg ttaaaaaggg
 99501  attttgtctt tctacactga ggctagggta tgtttaaaca aaatttgcct
 99551  acgatgtctt gggctaagga aaaatgtcac attatttatg acagatccaa
 99601  aacttttctt taaaaataca atggccaagt gcagtgcctc atgcctataa
 99651  tcccagcact ttgggaggcc aaagagagtg gatcacctga ggtcaggagt
 99701  tcgagaccag cctggccaac atattgtgaa acccctcta ttttaaaaat
 99751  acaaaaatta gttgggcgtg gtgctgcatg cctgtagtcc cagctacctg
 99801  ggaagctgag gcaggagaat cacttgaacc tgggaagcag aggttgcagt
 99851  gagctgagat cacaccactg cactccagcc tggacgacag agcaagactc
 99901  catctcaaaa aataaaaaat aaaaaaaaat acaagccatc aatctgaaga
 99951  agagcttttt aaatatagct caactgagca atagtgaaaa tactgtttca
100001  tcagttcttt ttggtacatt caggtacaaa ttactgttag tctcaactga
100051  gcctgctgtt ttttcctcta ctccaatcat aaaatacttc tttagcatca
100101  tttaatcact catttctttt cctctgaatt cccactaaaa cagtactaat
```

FIGURE 1AG

```
100151  ctcatatatg tggtggtaaa tgtgtttatt gatttcattc tattaaaaaa
100201  ttagttggaa aagtcatttt taaaatggga caagtttttt tctgttttga
100251  tataaattgt cattttcaga gaactgaatt tacctctgaa tccatctgtc
100301  cagaataagc caatattctc accttgaggt tttatgtggt tctcccttcc
100351  tccttgacca gattatcaaa tagtagtcag tcatcacatt gatacaagaa
100401  ggcttttcct tctatctacc taagttttat tgctacaaaa acagattata
100451  ttatctgagg ttttgagatt atctatacat cttgctgcct ctagttactc
100501  tgtcttctta atcaacaatg gttggctata tgcctgcttg atacttaagc
100551  ttccttaatg gcaatttaa aagctttgct agaacccttt cagatttctg
100601  agtagactaa agttgcttta ccaggtacct gtgagactgt tgtaaagatg
100651  catgtcttaa acgttaaggc aaaaatgata tttttatatt acattacact
100701  cttgtgctgt gagccaccga gtgctttttc tgaaccactc ctgtgtggtt
100751  ggcttttggg ggaaggggga gttctgaagc tgtgtgtggc tcttggagag
100801  aactctagaa ccctggtgga agactgtgtg ctcttatatt ttttctgcat
100851  ttatttttctg ttatttcaat tttctttctt ctgtgtgcaa tgaatgatct
100901  gcatgtgttg ttaaactaaa ctcaataaga ctagattttg gttttttttcc
100951  aacatagtca acttgtgtcc ttattggcaa aatgttccat tgtttcaaaa
101001  acaatctttc caaaatggtc tctccttctg ttcacattta ttgatagagg
101051  aaacggattt agtcttctaa caacacatca taggacttaa aataagaaac
101101  gtacttttct ttcgtttctt acaaaccagc aatctagaat cttttcttct
101151  gttttgttga acatatattc tatctgacaa ttggttacct atatcaacta
101201  taaatgcaga tgtttcacac aaaccaagaa cttacgtttt caaatttcaa
101251  caattaatgt catgaatttа ttgatttctg tagttattct ttgaagttct
101301  aaagtacgtt attaatcatt tatactatgt gttattgata tttattacag
101351  gggtagctat attctaaagt atttattctt acatgctaac acagagacta
101401  tcatcatttg tatgtaatgc ctagttcaaa tccaattttt caacctagcc
101451  gttaagatca ctggatatct ttcaagcagc acaattaaac aacatagtac
101501  tctctgctta aatagtctgt gtacttctat attaaaaaca ataaagccaa
101551  atggctttgt ttttataaaa gaatccctga gcactttcct attcgtgaaa
101601  tgcttagtaa tgtgctgctc tatttccctc actcctagta agttctgtag
101651  taataagcag aagctcttca gaatgtacac ctcacggaag cagaggtacc
101701  cagcatccgg gctattgaca tgagatttga gaatgccaac taacctcagg
101751  tgcatgacca ggttacaccg ccaccccacc tgagccctgt tcagagactc
101801  actctttcta gggacttctt gaatgaggtt ttcaacccgc ttgaaatttt
101851  ccttgttgcc tgttgcctgc tttgatactc tccaccgctg ggacaaatag
101901  tcggcgtccc gcgtagaact ggcagtcagc cctttggcgc ctccttgtgg
101951  ttggacaact gctgagctgc tgcacgcact ggattgttat ggctcagttg
102001  ccatattgtg cctgaggcga gaatttgtag aatgcttatc ccatgaaggg
102051  ctaaaaccct aattaagtat aacaataact acagcattct aagtcccaga
102101  ggattactgt ggggttatga tgatgccaca cagttgcctg gcagagaaca
102151  gccggtagta gactgcatgc taggccattt gaataacctg tacatctggt
102201  tcctagagat gagagaattc tctcttgcag ggtgacagtg caggctctgc
102251  tgagcgtggt cctcagctgt aactgtggga ctgtacccta agagagatgc
102301  tccgatcaat gaccacagca attttttttt tactttctgc aaagcaagac
102351  ctccttgttg gtctcttggg gataatcctt ggcattcttc ctaaaaatac
102401  tgttacataa atcttcaaaa atcatattcg tagatgtcac caaaaaaaag
102451  gcaggaaaat aatgaagact tcagtgtttc agtgaagagt ctatattttt
102501  aatcaattca atgtgtgttt tcagtaacag tcacctgatc agcttaatag
102551  tcatctaatc aagacgctgt gttgattttc aaagggaaac aaagtagaaa
102601  aataataaag tgagcttttt gtaagaggac acaagaacag atctttgcct
102651  tggaaaagaa aattttgcct ggttaaaaag ttcttgatta gaatcttatt
102701  cttaactttc atataattat gtcaaaagag aaagtgaaaa cattacattt
102751  tttctaattt aacatgtaat atgccgagtt tattttaaaa taattcttgg
102801  gaatctttaa aataatagac attagcaaat atccatgtag ttgagaagga
102851  caaaagggaa atgttactta gaatttattt ttgtcaactt taagtgcttt
102901  aaatgatact aagatttaga gaatattact cacattttcc aatttattca
102951  taaggtaatg tcaaaatggt tcatagaggc aatttttaaa aatattttta
103001  taggtatgat ttttaaaata cttttattat aaacaaacta tggtggattg
103051  aatgctaata ctttcatttt ggatgttttt actttttag taattgaatt
103101  tttttaattt ttcatattaa gtgtttttat gatggtttat ccatttctta
103151  tgtatttagt tgacatagaa aagagatata tcttgaaagt tggagaaaat
103201  aatttgatat taactaaaac caacctttta tagtaattag catctgttag
103251  ttccagaaaa ggtaatagat aaaatcaaat atagtgagga ccaattgtaa
```

FIGURE 1AH

```
103301  tgatatctat gtcaacttga gctattcatt aatctgaata aaggtgcaga
103351  agtgagcata tgcttcctga actagatcat tgtaaattta aattatggaa
103401  cagatgtgtt gaaactaaaa agagatttga aacttttaca atttaaaaaa
103451  aaaaaagctt gagaaaagta gatatttttg ggcaccatcc ctttgacaga
103501  tttgtttaaa taattgaagg ctttgggatg acatggaaaa cctagcctga
103551  gaattaaaag atgcaggttt atgatgttat tgttgctctt gtttaatgta
103601  atctatcatt taatcacaca tgtgtcaagc acagataaac tcttccactg
103651  ttgggattgt tgtaaagaac tcttgaaccc acctgacctc atcaccaaac
103701  tgccccgcct gttctttgca tgtgccttca gcgagtcatg ctggacttag
103751  ctgtgtctgc atttcagagg ggagctgtca gttgcatggt caacttgttt
103801  attgtttcca gaactccctg accaccagtt catgatttga tttgttttca
103851  tgtaaacaca cataaaacgt ggtgcccttt tagaatatcg tttgttaagc
103901  aactaggcat ggaaaaataa atgttactgt ttcttgttag ctacaaagca
103951  catatccact aaacacattt gctgttggca tgctgcagtt ggggacagtg
104001  gacattgcgg taagtggaca aaacaaggcc tccacttcgt ctcaaataag
104051  ccttatccat gagaacgctg ctttcatacc ccacaaaggc tgcggcttta
104101  ctctctcaga gtagctgctc tgagagactt ccctcagact cattgcccag
104151  gatttcttca ggccctgcag agtcctgggc ctctcacatt gatgacagta
104201  tcaccttcta atgaatggca taatttcact ataaaggaaa caagaaaaaa
104251  aaacagaatg ggtacacaaa gcttcttaca gttcatttga ttcccacaag
104301  aatcccttag ctgtgttgct atgtttatct ccaagttaga gatgagaacc
104351  ctagcccccg tgtgtctaat cccaacctgc ccttcctagc acatcatagc
104401  atatctcttg attaggaaag tgtgaagatg cactttggat tttatgattg
104451  ttgttaatgc ttcttttatc agcccacaac aatttgatct tagccggcat
104501  cagagaaccg aatgcctgaa caaatataat ttaccagtag ctgccacagc
104551  aaatcaataa cctgtttact agcaggaaat tgtgttagtg aacataacat
104601  ctcattctct tcatcagtca tcacattcat tatctgttgg ggctgttcta
104651  tcttgtgtgg ttttcatctc acaagaatga atgtaagcat aaaagaaatc
104701  taatgttaag tgttgtgtgt ttaatattat gtatgtggtg ctaccaactg
104751  ctatgagatt gcatgaattt atggataaca taatcttgcc tggaatataa
104801  aatgcatgcc aaatgtaggt atatatgtaa ctgtcatccc tgtttacctg
104851  tagaaatgtc tagaaattac aaagagatat gctcccaaac aaaaaataat
104901  tttttaaatc tcaaaagttg aggttaaagc taaaattacc caactgtttt
104951  tcaagtgaat tccaaaacag ttcttagtta tctacagtgt aattgtgtac
105001  aaaatgctgt atgacctcag tcttttctac aatgaatcca agaaggatgt
105051  atgtacctgt agaatgagat tgatctcgaa tgcaaatata gagattagat
105101  aaagctcaaa ttttaaataa gggaaaaata attgctatgc tcctacgtgc
105151  tgaaaacatc ttgtctattg aaatatatga ccacatgagc ttcatcaaat
105201  tacttaccca agcaaagtgg aagaaattgc ttgaaatgga ataatcatgc
105251  ctctgttctc cacagTCAGA AGCTAAGTTT TAAGGAGCGA GTGCGCATGG
105301  CTAGCCCCAG GGGCCAGAGT ATTAAGAGCC GACAAGCCTC AGTAGGTGAC
105351  AGGAGGTCCC CAAGCACCGA CATCACAGCC GAGGGCAGTC CCACCAAAGT
105401  GCAGAAGAGC TGGAGCTTCA ACGACCGAAC CCGCTTCCGG CCCTCGCTGC
105451  GCCTCAAAAG TTCTCAGCCA AAACCAGTGA TAGATGgtaa gccctgtttt
105501  tccataacca tttttaattg gataggctat agtgagtgag attatgaagt
105551  aattaattct ccatagtgcc acttgaagaa agaagaaaac aaccccagag
105601  aaagaattgt ttgtttgttt tattggaagt ttattcattg ccttgggcaa
105651  atgtacagaa cataagttta cttttggaaa ccactttggc agctaaattt
105701  acattccaaa gaagctgaca aaatgttgtt aattcttcac ttgtatctac
105751  aaatttattt ctcagacaag ggccacatta agatcaatgg gactgtcatt
105801  ctgatgtatt tgtgacgtct gaccagcaaa ggtccaagac ccagggacaa
105851  ccaggtgctt gctctgtgaa tatcttgaaa cacagtaagg aggatgatca
105901  tttctggtca acaatgaagg tgctctttcc ctctctcaca cactccatct
105951  accagcaaat cagagaccac tgcttatctt ccttagagag gttcctgttg
106001  aaagttattt cgaagtcttc caatgataag taaaattcaa gttcttctcc
106051  caagaggaat taacctattt tatttatcat attatgtagc agacattcac
106101  ttgccaacac attttattga gtgccacata attttcatgt ttataaaata
106151  aaatatttta tttttcattt aagataagct tggctttcct tttaactagg
106201  ccccctggga tctcttatac tgggcaagga accaaaatca aatagcattt
106251  cccattaatg cataaaaact acaaaggcta tcagtccttc tgttcccttt
106301  tcctaaataa cgtgtatttt cccaggccct caaagctcga ggaataaaat
106351  taacaaccag gggtcataat cacaatgatc tgaggatccc tgcagtgaag
106401  tccctggaac cgcagtccac gggtccctct cagcttactc aaaggtcctc
```

Exon 10

```
106451  agggatatct cttccacgct caagtgagca acacaagtca cctcttcacg
106501  cctcactcca caccccctgtg ggtgccatgc tcttcagggc gacccctagt
106551  ggctgcactg acgtggctcc tcctggcgga gcttgcaggt cccatatggg
106601  cgcaagacgg ctgatcctgc catgcttccc cgcagcctgt cctgtgctaa
106651  ggaaggaaaa acctccgcca ccaacacggg acactcctcc atcgagccac
106701  ttgcaggatc tgagtcactt gtggcacagc ttttcagtgt cctctagttt
106751  cctcactctc ctcctaggat tttggctgaa agcccttgag cagctgagtc
106801  aagagttacc agtgacaggg ctttatgttg cactcaaaat aggcttgctg
106851  aatataaatg ggtacatcct ttctggaggg caatttggca aaatatatta
106901  aaagtcttta catatgtcta agcctagaca catcccacct accaattcta
106951  tttctaggat ataatagata caatgaaaca atgtcaggca ttagaaatga
107001  tgctctaaat taaaaatttt tgacacagaa agatgataac aaaaaaatca
107051  ttccatttat atatattata taaattcatg tatctatagg aacaagtctg
107101  gaaagattta caagaatgtg tgaacagtta cctttgagtg gtgagatcac
107151  agttatattt tgtttcttca ttttttaatc tgtatttcct aatatttcta
107201  caatgaacag gtaa gctct tgtaataaga aggcaataaa ggatttttctt
107251  ttttaaaaaa aaaaaagccc tcagtttaga aaaacaaaat gttaggggga
107301  aaaaaagaaa aaaaaaacta gcccttcaag aaaaaaaatt agcccttcct
107351  ttcacacact gccctctccc ctgcccctac tctaggggcc cttgccctga
107401  ctgttactca cctaacacct ttccttaagc tgatttcctc ccaagtggta
107451  gaaggagcag cttgtcttaa tggtgggaac cagtctttgt tgagtgcaga
107501  catagactat gtaatgatgt ttaatagctt ctactacaaa tggaacttgt
107551  attagtttgc tcaagctgct ataacaaagt actagatgcc ttaaacaaca
107601  aaaatttatt ttctcacagt ctagaggcta gaaggccaag tttaaggtgt
107651  cagcagggtt ggttccttct gaaggctttc ttcttggctt tagatggtct
107701  tctccctgag tctttacata gacttttctc tgtacccagc catgtgcaaa
107751  tttcctctac ttataaggat accaatcata ttggattagg agccactcta
107801  ataacctcat tttaatttaa taacatctct aaagacccta tctccaaaca
107851  gtcgcattcg gaggtactag gggttaggac cataacatat gaattttgga
107901  gggatgcaat tcagcccata gacaaagctc atgctcaccc acatcacagc
107951  atccctggaa agctgagatg tgtccatatc ttcatccccg gccctggttt
108001  cacactgcat tagaaatcat acattacata ttgcaatgga tccatattct
108051  tctaacatgt gcttcaaaaa gcattcaact ttgtagtgta aggtccttac
108101  tgttggctga gcatatttaa ataaaaaatt catagaatct ggatttttaa
108151  tttggaaaac aaattctact tgtactgttt ggccagagga aaagaatttt
108201  tcacagtatc tagagtcacc actatctatc acaatatttt cagtatctgc
108251  aaagatgtct cagaggtaca gaaacagaag tcctattctc taccaaatca
108301  caaattggag aggtctcctg tcatctattt tctaggtcat ttcatacgag
108351  tacagttttg tttgtttaca aaagaattgc ttctcccttg ttgatgccca
108401  ttcaattaat tctgagtttc ccaagtgacc agaggaccaa ttgctgttct
108451  gttgaaatta ctttgttggc tacccacctg caagagatag tagctcctgc
108501  ctcctcattt aatccaatag tccagaatct ttacctctga ttgaattcaa
108551  tgttgcgtct tgggaaactg gaagttcttt ttttacaaga aaaaaaatta
108601  agtagctgtc aaataaatgt agacttcagt tatacatctt tacttatagt
108651  acctctttag gttttaagta tttctaaaat catctactta ctaccataga
108701  aaataatata taacacttat agccagtttt caattattcc aggtctattt
108751  gcccattcac ttctggggct gttttcttct cctctgctct cctcacatat
108801  tttcagcatt ccattgccca ttaacatgct caggagaata gacaaataaa
108851  agaaagaata atggaaactc agatcaacct ttaagttaat aacaaaaagt
108901  tatatttgga aaataataga cttgcaattg aaagatagta taatagagaa
108951  aaaaaaatat tcagggttaa tctgtaaatt ttaataattc ctgacaaatc
109001  tgatactctt tactacagac agtagtgttt tcataattta atgactcttt
109051  aagaaggtta ttaaatatcc atggcatttt tctcttgcta taatttttaa
109101  taagattaat atgttacact taaaaaggac gcagttgtct ctcaatattc
109151  catacttgtg tgtaccagaa aagtagaaag tagcaggcag atgctgaagc
109201  cacaaatgac aaacgaaaga aagtaaactc taaaggactg atgtggtgtt
109251  atcataccaa atttattttg actgctatga tatgaatcat atttttaact
109301  gataaattct ataataaaag atagaaatac tctattcatt gacagtatgt
109351  aaccctcttc acataatttt agaaattagg taatatagaa atatttttgt
109401  caagtatatg agtaataata atgataaaac gaacatgtat tgaattcttc
109451  ccattggcat gtgttgttct aaattcttta cctctattat tttatttaat
109501  tctgtcaata cccctatgga gtagctgagg tattatcccc attttatgga
109551  tgaggaaact aagagttgaa tctaagtaac ttgcccaagg tctagcaggt
```

FIGURE 1AJ

```
109601  ataagtaaag gagccaccat gcacatgcag gcaattgaat ttcacggtcc
109651  tcctacaaac gtattctaag atgttctcct agatattata tcaatttccc
109701  tttaagaatc tttcatttct tcccctcccc caacccccac caccctcttc
109751  ttgccgctgc tcttccaact tcaatcggtc agattccccc tcccatataa
109801  gccacttgac catgaccatg ccactatccc atctttctcc cagcctcagc
109851  tgccaaacct ctcaactaca tcatctcaag gcagccagag ctagaagatt
109901  aggcaaattg gggaaatggc ctttcaatga ccgttctctg ttttgatcaa
109951  gtatctggga agagactcag gataacagcc atactggtct gtgtctattt
110001  tccctggagg gaggccaatg gtagggtcat ctgaggcctg tttcaagatg
110051  caaaagatag tgtcagaaga tgcacaggtg ttgccaacag acaagcaagt
110101  ggaaggtggc agattgcaag cgagaaatgg agcaagcagc caaaatccac
110151  aagaatgata ctaaggtaga gctaggagaa aatcttcgga tttctggtga
110201  ctagtttgct acgaaggagt cctacactta ctgaacccca ctgcatttgg
110251  gagtgcctta cagaattgca atcaaagagt acaataacct ggacagtgaa
110301  ggagaaggac gtagctttag ggagctccac cttacagtgc ttgatattag
110351  ctaaacccaa cgttctgtag taattagcat gttcgttcca gaagtggcaa
110401  tagatctgaa aatctgtctc acatacatgt ataaccatgc atgttttaac
110451  aagtctaaca ttgtttctgc ttaaggagaa attaccattc ctgctgagca
110501  atcctcagtg ctcatgttag ctgccatgga aggtacatcc tcatcaggtg
110551  tttatgggaa aaactggcac agcctgggtt caggagatgt ttagggttca
110601  ccagggtggg atctgggtga gatgaagatg cagaatatct tccgattgtg
110651  ggggtccctc aaggctagtg cctttgttcc aggcactgat ggtaattcct
110701  ctctcttcac tacccttcat gttccctttct cctctcagcc agtgtaccaa
110751  ttaggatgca tttagcagca ggtcacaaaa gaagcagatt caactacctt
110801  aaactataat gcaatttata ataccacata gaaagaggct cagagataag
110851  acagctctcc acagagcctc agggctctgg cttcatttct ctgattctct
110901  gagtcttctt ttgacttttt ccatctgtct gcctgcctcc tcctcaggct
110951  ggaagcaaaa tggctacagc agttgcaata tcttctatag atgcaacact
111001  ttcagaggca gaaagaggcc atcttatgtt tgtatctctt cttaaaagtg
111051  aggagaactg tccattcaca tcttatttta cagaatcctc atgcctaaaa
111101  caatcaccag catggaggat gggaccgcca tcattggctg tcaccagtca
111151  ggacccagca gctggatctc ggccagactc ccctaaagca catgatcaag
111201  tgtgggggga agtagctgga taaatttaag gatttaggtt tggggattgc
111251  atttggggaa agcaactttc catagtataa tatttgatat agccaagaaa
111301  cctcttccac tttggggtga gggtaaggag tcagcatgtc cttaaacatg
111351  gtgctttctc tcaaatattc tgtctatatg tcatttctgt tcctctaaat
111401  gtccgggctt ttaaaaacat aaaagccaga tttataattt ttttcacttt
111451  tctctcatca catcatttcc atgaaacaac aagcatagac tagactgtct
111501  ccttgaattt caaatgaaag gcaaagtggg taaaggaaca actagcaaaa
111551  ataaataaat tagtatttca atcatataat ccttcctcac atacagtcag
111601  cccataaatg ttctatcacc accaccacta agggaaaact ggtacagttc
111651  ccttcctctc cacctcctca gcagcttcct gacacctcgc tcctcaagct
111701  gtttctcttg gtgactcctt cttccttctg aagttaataa ctaacccagt
111751  ctcacctaaa aatagcaaaa aagtagaaat acaccatgtg gggtgccaga
111801  accctcaagt cttcttaaag atagttcatc cccttcctct cttctcttaa
111851  cttctaccta ggttctaggc ccaccagtct accacaaccc ttgtttgaaa
111901  atatcaagat cactgaaaac agtgacaaaa aggcagcatt ttaatgcaat
111951  ggttttgaca actatcctga actaacagtc tcttgtatcc ataatggcct
112001  attttcttcc aagcagtata aatcacagac tatcagtatt ttctatttga
112051  ctaatttatg cacacgagct ttcatcttac actaatcctc ttttatgctt
112101  attttccaat ggcatcttcc tccctcatgt ttttctcagt ctccccagtt
112151  gacatttttg gtgtttccac aaaatgccaa gcaccacgct gcacatagca
112201  tttttcctga ctttccataa tgatggccca acttcagcca ggccttgatt
112251  ataattttcc acatgatgct tcctggcact ttctgaaatt gcctgataat
112301  gactctgcat tgtgttgaca gaaataattc ttgttaaagc agtatcctat
112351  tagggcttcc acttaacctg tttgtgcaga tttctggcct gggattctga
112401  ctgagtaggg cacccattcc tgtcatcctc tatttgtaac aaaatctgag
112451  ggtttttctt aatgttaaga acaaaaggat ttattgagaa tgactggatc
112501  taaactctag aaatttattc ttcatattta actctatatt cagcgtaatt
112551  gttggagtaa ttctatgcaa aaccctacaa agggtattca gtaggattct
112601  aaaacgcact ttcagtactt ccttaactta ttggtaaaaa ccattacctg
112651  aagaaattgt ctcaattctg atccataggt gtctttttte tttagttgtc
112701  caggttcttt attcagtccc tcaggcatct tcattcaaag acatatccta
```

FIGURE 1AK

```
112751  ctcctctgct gtgtttcata tgtactcttg tccccctaag atctgcttct
112801  cctattgggt ggagagtgac ctctcaatct ctggtttcag accccaagtg
112851  actacgttat ttcttggatt tctgagaaga gttgtgtctt agtttgtttg
112901  gactgctata aaaaacatac cataaactag gcagcctata aacaacaaat
112951  atttacttct cacagttctg gaagctggaa gtccaagatc atggtgctgg
113001  aagattctgt gtctggagag ggcccacttc cacgtgatgc aaagggcgag
113051  gttcctcttg ggtctcttta tgagggcact aatcccattt attagggctc
113101  tgccctcata gcctaaccat ctcccagagc ccccacctct taatactatc
113151  actttgaggg ttagggattt aacatataaa ttctgggggg acacaaacat
113201  tcagaccata acaggttgct tcttccatta ctttttgtga aatgcttgtt
113251  cttagttttt agtgacgggg aaatgctttt ctattttgat aagactgaag
113301  ttccacctgg ctttctactc taatccaagt gctctttgta ttatagaaca
113351  ggatttctgt cagatttctc taggttctgt cccatggttt gttgttactc
113401  tacagtgata aggaaaatta tattctgttt ctgttggtgg ataaaatagc
113451  ttcctgcttg agctctgaat ggatttcatc tcctcccttc cagcagaaac
113501  tgagctgcca aatgaccttc gagtgctgcc ttaaccatac cttttggctt
113551  ctgtagatcc aggtttcatt gagaaaccca gggttataaa ctggagccct
113601  atattttgtt tcatcagcaa agtgtgtgtg catgtccaca ttgatacttt
113651  aaaatgaatc tgaatgctgt attagttatc tattgttaca tagcaaatta
113701  ccctcaattt agtggtttga aataacacat acttataatc tcacagtttc
113751  tatggtcagg tatccagaag cagtttagct gaatggttat ggctcaaaat
113801  ctcatatgag gttgcagtca agctcttggc tggagatgct gggagaggac
113851  ccattaccaa gctcaactga gcatttgcta gcaggccttt tatttccttg
113901  ccacattatt cacaccctag gttgcctgaa tgtccatatg acatgcagct
113951  ggcttccccc agagagagct gagagagtac gcagagagaa gctgcagtct
114001  tttatgacat aagctcagaa gtgttatgcc atcgcttctt tcatgtgtaa
114051  gtggtcacaa agaccaaccc tgtacagtgt aggcagggac tatacagggg
114101  ggtaatacca ggagatgagg gccactgggg accatgttag agtcaggcta
114151  ccacaaatgc cttcagatag attatgtctt ttaaattgca gatttcaacc
114201  agtccctatt gtctttccag gaacccaaac caccaattcc ccattccttt
114251  cgacctctcc gttacctacc tgcctttaac gacatgggtt tataacttct
114301  ggtctaacca ttttatgtcc agtatccttt gtattatatc tcaaaaaaaa
114351  aaaaaaatcc tggcctcaac ctatagctac gcaattatat tccactctta
114401  gtgcagactc tcaaaaggaa tattaacaaa atattgagta tgtgattact
114451  gcagcaacaa gttaaataaa atgaggaggc caggtgcgat ggttcatgcc
114501  tgtaatccca gcactttggg aggctgaggg ggatggatca cctgaggtca
114551  ggagttcgag accagcctgg tcaacatggt gaaaccctgt ctctactaaa
114601  aatacaaaaa ttagccaggc gtggtggcgg gcacctgtaa tcccagctac
114651  tcaggaggct gaggcaggag aatcacttga atccaggaag aggaggttgc
114701  agtgagctga gattgcaccc ttgcactcca gcctgggcga caagagcaag
114751  actccatctc gaaaataaat aaataaataa attgagggag caggacatga
114801  actagtcagt tgcaaaacca aagtgtcata acttctaacg cagctctctt
114851  tcttgtacaa tgtatggccc ctcttcagct tttcaagagg ttgaagatat
114901  gttcttggtt gcttcaaagg gcagaagcag aactaaaagg tgtgtgatac
114951  caatatttag ttcaatataa tggcagctta gcacttagag actccacagc
115001  aattgagtgg attccataat tggaagcatt caaatcaaag ttggatgatc
115051  aacagtcagg aatttctgga agcttaagga gatcaaacca gaaaacctct
115101  aagaaatttt cttccaaatc tgagtttttа taatctgctc ttctggacca
115151  atgcaaagta tcttccttag ccattaactc gtatcctcac tagcaattct
115201  atactaagaa atagaagagg aaagcaagga ttggctgagg aatgccagga
115251  gtgagttttc tgtccttacc ctagtttcac gtctctttga taccgagaaa
115301  agtgctaccc gctgcttctt gcctctcatt cctcccactg tttcttttcc
115351  actttcactg tcagccatag tcctttctgt cctaagaagt gtatcaggtg
115401  tgtcccaccc accattgtga ggtttatgtg tgtgctccat agcggctcat
115451  tcttagaact tgaataagcc ctccactgga tttcaattca tatcagaagg
115501  tatttgaggg ctgctactca gagctagcat gtttctgggc atttagaagg
115551  cagggaggag gcgtgacaac tgtcacccca aagaacttac tgtttgtctg
115601  taagttttac caccccagcc cacctcagtt acagtattga ttggcactga
115651  ggggaacaaa aggcaccttc ctcattcttc agacttcata gttttcagaa
115701  ataacctgtg ggtgacgtcc aaaattcgca caaaataagc acaaaattaa
115751  ccattacaca aatcacagaa tttagcccat atttaagaga agcacttttc
115801  agctgcatgg tgatttttcc ttcatatatc tcaaattatt tccttcaaag
115851  tcacacttag ttgtctgctg cataaacaga aaccaatatg acacaatttt
```

FIGURE 1AL

```
115901  aaaattatat ttaatcgctt tcatggtgtg ctctacttgg taaagaaggg
115951  gggaaacaag gttaagtaaa ggccaggatc ctttttctgc aatggatgac
116001  tgacatggga aagagatgag ttacccaggc tttgcttttt gctacctgca
116051  gtataaaact ccctgacatt gtcccaaatt gcttttacag gtatttttatt
116101  ttcaacatct aatttgttcg gcttttcttc ccttgccatc tttttcttct
116151  tttgccatgt ataatgcata acaacaattt ctgaactcca aaagcataga
116201  aacctcagaa taacattacc tgggaaaaat taatctctct acctccagct
116251  accaagagaa tcatttgcac atgaaaccct gagatttgcg tctttcatta
116301  atctaatgca gtagcaattg ttataccaca tcgttctatt ggaattgatg
116351  actaatcatt cccaaaactc ttttgaaact attgttccca taattttgtg
116401  ttttgattga aaaatgtcat gaccctatat ctcttcatgt tatctgttgc
116451  atagctaacc ctctccctca gatttagtgg cttaaaacag caaccatttg
116501  tttagcccac aattctgtta ggcagttctt ctggtcttaa gtgaactgac
116551  tcatgctctg tgttcagctg ctgtgttggc tggtgctgac tggactaagg
116601  tggtctcagt tagaattact gctctttgct catgtggtct ctcatcctcc
116651  agcaggctgg gctggttcac atggtggtgg tgggttccca agagcagtac
116701  attgatatct gaaggcctct tgaagttcag gctcaaccta tcacagtata
116751  atgtccacta tgtcctgttg gtcaaagcaa atggcaagga cagcccacat
116801  gcaagagaca gagaaagaga ttccacctct tcatgtgaga agctgcaagt
116851  gtcgtggcca gtattgcaat ctaccatccc agccatttaa agcttatttg
116901  cttttagtat tttcaacatc ctgttggttc tatgaagaca gtgtcagtgt
116951  ctaattgact tttttatttc tccctgtagt atccttcact caaagagcct
117001  aagaaagaaa aggaaaatag cattgttagc acctcatgta tcgaggcatt
117051  ggctagacat tttctatgaa ttggctcatt taatacacac atagccattt
117101  tgcagataag gaaattgaga ctcagaaaat gtaaataact tgcccacata
117151  attcagtcta aatgccaaaa ctggggtttg aagttgcact taggtctaag
117201  ttcaaagctt tttatgttct accatgcatg ctgcttagca tgttttcttt
117251  catataattc atgctgctaa tgaaacagta taaaccagct gtatgttaac
117301  tgctagtgaa atgatttatt gtcttctttt tcagtaaata tggcaagtct
117351  gctcaattta ttcccttttat cattgcatac actacaaata ttctctccct
117401  ataccttcac atgtcaatta aggtatgcaa cagtaatttc catttttttt
117451  aaacaatgct tatgttacca tctctagaca agttagtcca gatgattttg
117501  gggttaacat gttggcattt cctggcacta ttactgctag ctgaataaga
117551  gttgaaagtt ggggaaaaat ttaccagatc tgtattagtt ttttcgcaca
117601  ctgctataaa gaactacctg agactgggtg atttataaag aaaagtttaa
117651  ttgactcaca gttccacaac ctgtacagga agcacgcctg ggatgcctca
117701  agaaacttac agtcatgtca gaagagcgaa agggaaggaa gcgtgtcttt
117751  acgtggtagc agaagagaaa gagacagaga gaatgagaaa gtgagagtga
117801  agggggaagt gccacacttt taaaccataa tccaccccca tgatccattc
117851  acctcccacc cagtccctcc cccaacattg ggaataacaa ctcaacatga
117901  gatttgggtg gggatacaga gcgaaaccat atcaagatct atttagaatt
117951  ctccagcaga tttgattaac aatatagatt tgtgattctg caatttgtag
118001  ggtcattata aaacatggct gccttgattg caatcagata tctctgaata
118051  tggttcaaag gaaacagatc tcgttcttgt ggagatagga ttacataact
118101  ccctctcagt cattttgcca ttgattcaga atgtttctcc ctaagatgaa
118151  gtactgtttt agcttagaat ggtaacagca attcatcacc aggcacagtg
118201  gctcacacct gtgatcccca cactttggga ggcccaggcc tgtggatcac
118251  ttgagcccag gagttagaga ctagcctagg caacatggca aaaccccatc
118301  tctacaaaaa atgtaaaaat tagctgggca tggtggcaca ggcctatagc
118351  cccagccact tgggaggctg agaaatggga ggatcttttg agcccaggag
118401  gttgaggctg cagtgagcca tgatcgcatc actgcactcc atcctgggca
118451  acagaacaag tccctgtctc aaaaaaaaaa aaaaaaaaaa aaaaaaagca
118501  attcattgat ctcatctagt ttgactagtt caattataca tgtgagaagg
118551  ctatctgaga tgatgtcagg tgtggagcag tgactatccc agtgatctga
118601  atgtgattga ccacttggct tcaccaggat tatctcactg tttggttcta
118651  ataaaggcag tcattctagt ctatgagttt acctcccttt tgctacaaac
118701  acttcagtga tatactattg aaactataaa aatccataaa aattggtttt
118751  tgtatgtgag ttttaaaaaa ttgttttcac caggctgtga gttttatgtc
118801  tttgttttct attgggatac taatagtgct atgactatag tatgttctca
118851  aggaaattct tatgaaaatt gaattaatcc gacacagtgc atggttttgg
118901  agtaaaacag aacttgtttt aaatcctagt tcccccacta ggttgggtga
118951  gatgagacaa acgacttaac ctcactgcca ctttaatttg ttctctctct
119001  ctctttaggg tggtagaaat gatacctacc taatagggtt acgtgagtaa
```

FIGURE 1AM

```
119051  taataagata taatgtgtgt aaaattcttg tacaatgccc agcacagaat
119101  aggtgctcaa tatattaaat atattgttat tatttattaa ttaattaatg
119151  ctgatttctg cattaatttt gactaattga aatcctggac ttgcttaatt
119201  tgcatgtatt tgtcttccct tcttccagta cttgatggca atttctacct
119251  gtggtaaatg gaacgttaaa agttatatgc ttatacaaac tttagtcctt
119301  tattccttgg agtgagtttt aagagtcctc atgttgaata attcatgtaa
119351  tcacagaaat aatactatgt atcagggacc gcttccttta ttaaagataa
119401  aggcagtgga aatactgcct ttgtcagaaa tacttcagtt actctgagag
119451  agagagacat ttgtttacta tatgacagca cagtgcatgg caaataatag
119501  aagtttggaa aatatttatt ttgaatgaat gaataatgaa cacattgtga
119551  acaaataaat ggtttactat ttaattattc aggaatcaat taagctttat
119601  taataaaaat tgtttggggg ttttaaaaag cccacacaca aatgagaggc
119651  atcacagagg caaacggtat gacattatta aaatcgttat tgctgaatca
119701  cagttcagca ataagcaagt gtttgaggca ttcaaataag tgagtatttg
119751  agtgactcta agaagataat gaaactcctc cactgtttta cagttgcaat
119801  aatttttaag gaacatataa aaacatattc tagtgtttcc atttgaataa
119851  agatagtata tataacatat gcaattaaaa agaagaaaga aaacaaattt
119901  taatgtgttt ttcttttcac cttatgggca gttactagat gtatnnnnnn
119951  nnnnagcttc atcttgcccg tagaaaacag ttcagaaaag tattcatatt
120001  taaaactggg gaggctgtag aaaaagaaga aagaataata ttggcaagac
120051  aattggctga ccttatacat atcttggttt atcagcttac tctgtgagta
120101  tcccgccatt tccacgtgag aaaaattcag caacatgttt caaattgcgg
120151  atggtggtgt tatttaactg gcaatattct cttgcagCTG ACACAGCCCT
120201  TGGCACTGAT GATGTATATG ATGAAAAAGG ATGCCAGTGT GATGTATCAG
120251  TGGAAGACCT CACCCCACCA CTTAAAACTG TCATTCGAGC TATCAGgttg
120301  gtgaaaatct tgaacaacgt gattcagaga catacttatg attaattgaa
120351  ttactatgtt gctaagttct ttttctgcag gtaaatatcc tggaataacc
120401  actttccctt tcctattcat nnnnnnnnnn aatagagtgt tttgcaaaca
120451  catttgtatc tcaaaaatgc atgtagttcc ataaaagacc attttaacag
120501  cctttatatt ttttaaggga tgctattact agatgttgta tcttggactt
120551  ctggagattg catggaaaag ttagaattgc attttgactt taacttacat
120601  tcagggtttc aacggacatt aaaaaggcaa aacacttagt gttcagcctc
120651  ttttttagtg tgtttttcta ttcttaaggt gttgtctcac atgagatgtt
120701  cttaaattgt ccactgtaat ctcaggcttt tatattacac atctgcagaa
120751  gccaaaaata atttgatgca tgacttttcc ccccagagtt tcttattata
120801  tttactggta aactattttg gtaacttata ttaacagagt tataaagatt
120851  aatatgtaat atgttctcat acagAATTAT GAAATTTCAT GTTGCAAAAC
120901  GGAAGTTTAA GGAAACATTA CGTCCATATG ATGTAAAAGA TGTCATTGAA
120951  CAATATTCTG CTGGTCATCT GGACATGTTG TGTAGAATTA AAAGCCTTCA
121001  AACACGgtaa gcaatggaaa tgtcattcct tgtaaaggaa tgggcataga
121051  acctatctag gaagaacttc tctttagtag agtaaacctc tgaactccat
121101  atttttcatt catttttagt gggcaaatgg aatttgcttt aaacattgat
121151  tttatttttgc ttttaacata gatataactc aggcattcaa agcatccaac
121201  tgtctcattt tccttatctg taaaaatggg aagaaagtta gttcttgcct
121251  tatagggttg tcatgaggat tgaacaagtt aatgcatgta attcataaca
121301  tgtaacaggc ctggtactgt gtctaataaa catcaatggt tgttgctgat
121351  gtttgaatta ttactgctgc tgatcctaaa ttatctaaat tccatttatt
121401  atctaaattc taatcatcct ttgggaataa cgtactattt ctccttcatt
121451  aagtttcatc caaccatcca acctgtgaag acgggccttt ctctgacctt
121501  tatacagtag cagagtctac tgcagagcac aagagcactc agaatctcgg
121551  tgtgctgggc caaagttgag acttggccct tgtgttgttt cctggttgca
121601  agtgtgttca ccttgctctg gactaagact gaggtccttc attcatgtcc
121651  tgtacggttc tacaaatata ctatcctcct agtagcatct tattgagtga
121701  ttaaaagaaa tgaattccac atgttaattc caaccacata tggttgattg
121751  tgattatctc aaagccaaaa tattcagtaa attcagtttt ttaagagcct
121801  tgctttatta ccagcacaaa ttaccagcat ttgtgattgt atagtgccca
121851  aaatgcaagg actgagactt gacttttttt tatgcccccc agcacactta
121901  gcccagtgtg aggcataTaa tgggccctta gtaaaatacc tgttcatcaa
121951  ttgttataga aataacaatt tgttaattca tttagcaggt aattattgag
122001  cccatcatgt gtgccaggac ctgtggacat ccagagattg ataaaataat
122051  gacccagacc ttgtagagtt tgcagtttag taaattagat gnnnnnnnnn
122101  ngaacatctg aacatgacca gagattgtgg tcatattgca atctctgcct
122151  agatggccat ggccttctaa gttctttaat aaaactgtct acagctccca
```

Exon 11

Exon 12

```
122201  aggttttata aagttgaact gctacagaat ttatagaacc aatcttgggt
122251  ttctagctca tgtatcttct ccaacttgaa ctccgaaaga aaaagaccat
122301  ggctttctta tctgcttatc tttcacacat gtacaataga tgctcataga
122351  ataatctgtt ctattaatgt aagatctcta tagttatgat ttttgtcata
122401  ttttgaaatg gttaaattca ggaactgcct gatcagaggt agaaacatat
122451  tactttgtag tttaggacac ttttacttcc agaagatcac ccataagtga
122501  tttcatcttg gaccagaata atgagaaaat taatttcatg tgtaatctca
122551  tgttcaaata agcatatcaa ctggaacaag ttctttctta tttcatctta
122601  cataaattga agataactgt atttaatttt tttttccaaa actcttcatt
122651  ctgacctagg gcaatctcca ccttcagccc tcataatcag atctcctctt
122701  tctctgatag TGTTGATCAA ATTCTTGGAA AAGGGCAAAT CACATCAGAT
122751  AAGAAGAGCC GAGAGAAAAT AACAGCAGAA CATGAGACCA CAGACGATCT
122801  CAGTATGCTC GGTCGGGTGG TCAAGGTTGA AAAACAGgta caactcaact
122851  acgctgggta tctttttagc cagaattttt ttaatcaaaa tttattatag
122901  gcaattgtat gtattccagt gattatttta aaataaataa aatcacaaaa
122951  agagtgaata aaattaaatt ttctttgtgt gtagacagtg ctctctgaaa
123001  cactctggat ttccctttaa ggaatagaaa atctcatctc atcaattaat
123051  agttaattgg aaacaactat agatttccaa tagttgaaaa tcgtttaaaa
123101  ataacaaaga tctattcttc atttgtgttt cagttgtttt tattgtttct
123151  tttttaggtc attaattttt ttttttttt tttnnnnnnn nnngggacta
123201  tgggcatgca ccaccacacc tggctgattt ttgtattatt tttggtagag
123251  acgaggtctc accatgttgc ccaggctggt ctcaaactcc tgggctcaat
123301  tctcctgcct cagtttccca aagtgctggc attacaggca tgagccactg
123351  cacccagcct ggaatggaaa gtcttaaagt tgcattttta tagtgcttat
123401  atgacttta agaggcacta tttaaagaag tggtgggga gagatgctaa
123451  taaagactgt atagaagcca aagtgtccct ctcttcctaa gtcctcctct
123501  ggccccatca ttgctaaatg ttacattcac taagggtcaa gactgcatcg
123551  tactttatat tcaatatttc tttaaatgtg ttggcacacc ttgacttcat
123601  ttttcaaaat taaaaaatga agtccattct taataacaga ttatactcat
123651  gtgtaaccat tttcctcact tctagGTACA GTCCATAGAA TCCAAGCTGG
123701  ACTGCCTACT AGACATCTAT CAACAGGTCC TTCGGAAAGG CTCTGCCTCA
123751  GCCCTCGCTT TGGCTTCATT CCAGATCCCA CCTTTTGAAT GTGAACAGAC
123801  ATCTGACTAT CAAAGCCCTG TGGATAGCAA AGATCTTTCG GGTTCCGCAC
123851  AAAACAGTGG CTGCTTATCC AGATCAACTA GTGCCAACAT CTCGAGAGGC
123901  CTGCAGTTCA TTCTGACGCC AAATGAGTTC AGTGCCCAGA CTTTCTACGC
123951  GCTTAGCCCT ACTATGCACA GTCAAGCAAC ACAGGTGCCA ATTAGTCAAA
124001  GCGATGGCTC AGCAGTGGCA GCCACCAACA CCATTGCAAA CCAAATAAAT
124051  ACGGCACCCA AGCCAGCAGC CCCAACAACT TTACAGATCC CACCTCCTCT
124101  CCCAGCCATC AAGCATCTGC CCAGGCCAGA AACTCTGCAC CCTAACCCTG
124151  CAGGCTTACA GGAAAGCATT TCTGACGTCA CCACCTGCCT TGTTGCCTCC
124201  AAGGAAAATG TTCAGGTTGC ACAGTCAAAT CTCACCAAGG ACCGTTCTAT
124251  GAGGAAAAGC TTTGACATGG GAGGAGAAAC TCTGTTGTCT GTCTGTCCCA
124301  TGGTGCCGAA GGACTTGGGC AAATCTTTGT CTGTGCAAAA CCTGATCAGG
124351  TCGACCGAGG AACTGAATAT ACAACTTTCA GGGAGTGAGT CAAGTGGCTC
124401  CAGAGGCAGC CAAGATTTTT ACCCCAAATG GAGGGAATCC AAATTGTTTA
124451  TAACTGATGA AGAGGTGGGT CCCGAAGAGA CAGAGACAGA CACTTTTGAT
124501  GCCGCACCGC AGCCTGCCAG GGAAGCTGCC TTTGCATCAG ACTCTCTAAG
124551  GACTGGAAGG TCACGATCAT CTCAGAGCAT TTGTAAGGCA GGAGAAAGTA
124601  CAGATGCCCT CAGCTTGCCT CATGTCAAAC TGAAATAAGT TCTTCATTTT
124651  CTTTCCAGGC ATAGCAGTTC TTTAGCCATA CATATCATTG CATGAACTAT
124701  TTCGAAAGCC CTTCTAAAAA GTTGAAATTG CAAGAATCGG GAAGAACATG
124751  AAAGGCAGTT TATAAGCCCG TTACCTTTTA ATTGCATGAA AATGCATGTT
124801  TAGGGATGGC TAAAATTCCA AGGTGCATCG ACATTAACCC ACTCATTTAG
124851  TAATGTACCT TGAGTTAAAA AGCCTGAGAA ACCAAACACA GCTAATGCTA
124901  TGGGGTGTAT GAATATGTCA AGTTTAGGTC ATTTAGAAGA TTTGACACTG
124951  TATTTTGAAA TTATGGGAGT AAACACCTTC AAATTTCAGG CATTTCTGCT
125001  TTGTGACTAA ATACAAACTA CATTTTCAAG ATTAGGCCAT AATGTATATT
125051  TAAACACAAT GGCTATCAAC AGCTGCTAAT AAGGTATCAA CTAAAGCAGA
125101  ATTGGGGAAT AATAGAAATG GCTGCTTATT TCAAGATATA TTTGCCAACC
125151  CATTCCTATT CAGTCATTTT ATTATTAATG TAATTTGAAT GTCAATTTGT
125201  GTGCTTTTGG TGATTTAGCG CTGTGGCAAG CAATTTTGCA CATCATTTTC
125251  ATGTTGTTCT TTATGACAAG AATGTTCTTC AATTAGAAAA TGTGCAAATA
125301  ATGAAATTCA GGGCCAGTGA GGCAAATAGA CTATCTGACA TATTTGACTT
```

Exon 13

Exon 14

```
125351  TATGAAAACA TATTGCCTGA TGGCAGAATC AACTTTATAA GTGGTCAACT
125401  TCTACACAAG CGTATGAAAT ACTGGTCAGT AGAACAGCCA TTGTGATTGG
125451  ACTGGTTTCT CTGCAATGGC GCCAACCCCA GGCTTGCCAA TACTGCCTAT
125501  GTAAAGGGCA AGTGTGAGAA GCTATTCTCA TTTCGCTGAC ATACAGGTAG
125551  GACTATGGGG GATGGGACAT TTGAGTGGGA CTGAGATAGG AAAGGCTTGA
125601  AAAGAACCCA GAAACACCAC CAGGAAGTTG GCAAAGTAAA AGAAAATGAC
125651  TTCCCCCTCA AAGGGCAATG AGAGGGAGAG AAACAAACCA AAATAGAAGA
125701  ACTAGACTTT TTAGAAAATG AGTATTGCTA GGGAATTCAA CTACCTAATC
125751  TTCCCTTATT CTTATATATA AGCAGAGAAT TTTTGCAAGG TATTTATTTT
125801  TTAATATGCC CTGAATGTCT TTTGCTATTA TGTGTACATT TTGCATATGA
125851  AAGTCTAAAA CGAAAGTTCC TTTACTTTTT ATACTGTAGT GAAAATTTTC
125901  TATTCTTCCC AAGAATGTTG TCCCAAATCT GAAATTACTG GTTCAATTTC
125951  CTGATATAAA
```

FIGURE 2A

KCN6q cDNA

```
   1  CTGGAGTGAGGCGCGGGAAGATGCCTGGTCCTTGCCTCGCGGACTTGGCA   50

  51  GCCGCGTCCTGCGGGTCTGTCCACTGAACTGCTGAGGACTGCGGCGGTGG   100

 101  CCTGAGGGAGAGCCGCCGGGGCAAGCAGGGGGCCCGGATGAGCCTGCTGG   150
   1                                      M  S  L  L  G     5

 151  GGAAGCCGCTCTCTTACACGAGTAGCCAGAGCTGCCGGCGCAACGTCAAG   200
   6    K  P  L  S  Y  T  S  S  Q  S  C  R  R  N  V  K    21

 201  TACCGGCGGGTGCAGAACTACCTGTACAACGTGCTGGAGAGACCCCGCGG   250
  22  Y  R  R  V  Q  N  Y  L  Y  N  V  L  E  R  P  R  G    38

 251  CTGGGCGTTCATCTACCACGCTTTCGTTTTTCTCCTTGTCTTTGGTTGCT   300
  39  W  A  F  I  Y  H  A  F  V  F  L  L  V  F  G  C  L    55

 301  TGATTTTGTCAGTGTTTTCTACCATCCCTGAGCACACAAAATTGGCCTCA   350
  56    I  L  S  V  F  S  T  I  P  E  H  T  K  L  A  S     71

 351  AGTTGCCTCTTGATCCTGGAGTTCGTGATGATTGTCGTCTTTGGTTTGGA   400
  72  S  C  L  L  I  L  E  F  V  M  I  V  V  F  G  L  E    88

 401  GTTCATCATTCGAATCTGGTCTGCGGGTTGCTGTTGTCGATATAGAGGAT   450
  89    F  I  I  R  I  W  S  A  G  C  C  C  R  Y  R  G  W   105

 451  GGCAAGGAAGACTGAGGTTTGCTCGAAAGCCCTTCTGTGTTATAGATACC   500
 106    Q  G  R  L  R  F  A  R  K  P  F  C  V  I  D  T     121

 501  ATTGTTCTTATCGCTTCAATAGCAGTTGTTTCTGCAAAAACTCAGGGTAA   550
 122  I  V  L  I  A  S  I  A  V  V  S  A  K  T  Q  G  N    138

 551  TATTTTTGCCACGTCTGCACTCAGAAGTCTCCGTTTCCTACAGATCCTCC   600
 139    I  F  A  T  S  A  L  R  S  L  R  F  L  Q  I  L  R   155

 601  GCATGGTGCGCATGGACCGAAGGGGAGGCACTTGGAAATTACTGGGTTCA   650
 156    M  V  R  M  D  R  R  G  G  T  W  K  L  L  G  S     171

 651  GTGGTTTATGCTCACAGCAAGGAATTAATCACAGCTTGGTACATAGGATT   700
 172  V  V  Y  A  H  S  K  E  L  I  T  A  W  Y  I  G  F    188

 701  TTTGGTTCTTATTTTTTCGTCTTTCCTTGTCTATCTGGTGGAAAAGGATG   750
 189    L  V  L  I  F  S  S  F  L  V  Y  L  V  E  K  D  A   205

 751  CCAATAAAGAGTTTTCTACATATGCAGATGCTCTCTGGTGGGGCACAATT   800
```

FIGURE 2B

```
206   N  K  E  F  S  T  Y  A  D  A  L  W  W  G  T  I    221

801  ACATTGACAACTATTGGCTATGGAGACAAAACTCCCCTAACTTGGCTGGG  850
222  T  L  T  T  I  G  Y  G  D  K  T  P  L  T  W  L  G  238

851  AAGATTGCTTTCTGCAGGCTTTGCACTCCTTGGCATTTCTTTCTTTGCAC  900
239   R  L  L  S  A  G  F  A  L  L  G  I  S  F  F  A  L  255

901  TTCCTGCCGGCATTCTTGGCTCAGGTTTTGCATTAAAAGTACAAGAACAA  950
256    P  A  G  I  L  G  S  G  F  A  L  K  V  Q  E  Q    271

951  CACCGCCAGAAACACTTTGAGAAAAGAAGGAACCCAGCTGCCAACCTCAT  1000
272  H  R  Q  K  H  F  E  K  R  R  N  P  A  A  N  L  I  288

1001 TCAGTGTGTTTGGCGTAGTTACGCAGCTGATGAGAAATCTGTTTCCATTG  1050
289   Q  C  V  W  R  S  Y  A  A  D  E  K  S  V  S  I  A  305

1051 CAACCTGGAAGCCACACTTGAAGGCCTTGCACACCTGCAGCCCTACCAAG  1100
306    T  W  K  P  H  L  K  A  L  H  T  C  S  P  T  K    321

1101 AAAGAACAAGGGGAAGCATCAAGCAGTCAGAAGCTAAGTTTTAAGGAGCG  1150
322  K  E  Q  G  E  A  S  S  S  Q  K  L  S  F  K  E  R  338

1151 AGTGCGCATGGCTAGCCCCAGGGGCCAGAGTATTAAGAGCCGACAAGCCT  1200
339   V  R  M  A  S  P  R  G  Q  S  I  K  S  R  Q  A  S  355

1201 CAGTAGGTGACAGGAGGTCCCCAAGCACCGACATCACAGCCGAGGGCAGT  1250
356    V  G  D  R  R  S  P  S  T  D  I  T  A  E  G  S    371

1251 CCCACCAAAGTGCAGAAGAGCTGGAGCTTCAACGACCGAACCCGCTTCCG  1300
372  P  T  K  V  Q  K  S  W  S  F  N  D  R  T  R  F  R  388

1301 GCCCTCGCTGCGCCTCAAAAGTTCTCAGCCAAAACCAGTGATAGATGCTG  1350
389   P  S  L  R  L  K  S  S  Q  P  K  P  V  I  D  A  D  405

1351 ACACAGCCCTTGGCACTGATGATGTATATGATGAAAAAGGATGCCAGTGT  1400
406    T  A  L  G  T  D  D  V  Y  D  E  K  G  C  Q  C    421

1401 GATGTATCAGTGGAAGACCTCACCCCACCACTTAAAACTGTCATTCGAGC  1450
422  D  V  S  V  E  D  L  T  P  P  L  K  T  V  I  R  A  438

1451 TATCAGAATTATGAAATTTCATGTTGCAAAACGGAAGTTTAAGGAAACAT  1500
439   I  R  I  M  K  F  H  V  A  K  R  K  F  K  E  T  L  455

1501 TACGTCCATATGATGTAAAAGATGTCATTGAACAATATTCTGCTGGTCAT  1550
456    R  P  Y  D  V  K  D  V  I  E  Q  Y  S  A  G  H    471
```

```
1551  CTGGACATGTTGTGTAGAATTAAAAGCCTTCAAACACGTGTTGATCAAAT  1600
 472  L  D  M  L  C  R  I  K  S  L  Q  T  R  V  D  Q  I   488

1601  TCTTGGAAAAGGGCAAATCACATCAGATAAGAAGAGCCGAGAGAAAATAA  1650
 489   L  G  K  G  Q  I  T  S  D  K  K  S  R  E  K  I  T  505

1651  CAGCAGAACATGAGACCACAGACGATCTCAGTATGCTCGGTCGGGTGGTC  1700
 506    A  E  H  E  T  T  D  D  L  S  M  L  G  R  V  V    521

1701  AAGGTTGAAAAACAGGTACAGTCCATAGAATCCAAGCTGGACTGCCTACT  1750
 522  K  V  E  K  Q  V  Q  S  I  E  S  K  L  D  C  L  L  538

1751  AGACATCTATCAACAGGTCCTTCGGAAAGGCTCTGCCTCAGCCCTCGCTT  1800
 539   D  I  Y  Q  Q  V  L  R  K  G  S  A  S  A  L  A  L  555

1801  TGGCTTCATTCCAGATCCCACCTTTTGAATGTGAACAGACATCTGACTAT  1850
 556    A  S  F  Q  I  P  P  F  E  C  E  Q  T  S  D  Y    571

1851  CAAAGCCCTGTGGATAGCAAAGATCTTTCGGGTTCCGCACAAAACAGTGG  1900
 572  Q  S  P  V  D  S  K  D  L  S  G  S  A  Q  N  S  G  588

1901  CTGCTTATCCAGATCAACTAGTGCCAACATCTCGAGAGGCCTGCAGTTCA  1950
 589   C  L  S  R  S  T  S  A  N  I  S  R  G  L  Q  F  I  605

1951  TTCTGACGCCAAATGAGTTCAGTGCCCAGACTTTCTACGCGCTTAGCCCT  2000
 606    L  T  P  N  E  F  S  A  Q  T  F  Y  A  L  S  P    621

2001  ACTATGCACAGTCAAGCAACACAGGTGCCAATTAGTCAAAGCGATGGCTC  2050
 622  T  M  H  S  Q  A  T  Q  V  P  I  S  Q  S  D  G  S  638

2051  AGCAGTGGCAGCCACCAACACCATTGCAAACCAAATAAATACGGCACCCA  2100
 639   A  V  A  A  T  N  T  I  A  N  Q  I  N  T  A  P  K  655

2101  AGCCAGCAGCCCCAACAACTTTACAGATCCCACCTCCTCTCCCAGCCATC  2150
 656    P  A  A  P  T  T  L  Q  I  P  P  P  L  P  A  I    671

2151  AAGCATCTGCCCAGGCCAGAAACTCTGCACCCTAACCCTGCAGGCTTACA  2200
 672  K  H  L  P  R  P  E  T  L  H  P  N  P  A  G  L  Q  688

2201  GGAAAGCATTTCTGACGTCACCACCTGCCTTGTTGCCTCCAAGGAAAATG  2250
 689   E  S  I  S  D  V  T  T  C  L  V  A  S  K  E  N  V  705

2251  TTCAGGTTGCACAGTCAAATCTCACCAAGGACCGTTCTATGAGGAAAAGC  2300
 706    Q  V  A  Q  S  N  L  T  K  D  R  S  M  R  K  S    721

2301  TTTGACATGGGAGGAGAAACTCTGTTGTCTGTCTGTCCCATGGTGCCGAA  2350
```

```
722  F  D  M  G  G  E  T  L  L  S  V  C  P  M  V  P  K   738

2351 GGACTTGGGCAAATCTTTGTCTGTGCAAAACCTGATCAGGTCGACCGAGG  2400
739   D  L  G  K  S  L  S  V  Q  N  L  I  R  S  T  E  E   755

2401 AACTGAATATACAACTTTCAGGGAGTGAGTCAAGTGCCTCCAGAGGCAGC  2450
756   L  N  I  Q  L  S  G  S  E  S  S  A  S  R  G  S    771

2451 CAAGATTTTTACCCCAAATGGAGGGAATCCAAATTGTTTATAACTGATGA  2500
772  Q  D  F  Y  P  K  W  R  E  S  K  L  F  I  T  D  E   788

2501 AGAGGTGGGTCCCGAAGAGACAGAGACAGACACTTTTGATGCCGCACCGC  2550
789   E  V  G  P  E  E  T  E  T  D  T  F  D  A  A  P  Q   805

2551 AGCCTGCCAGGGAAGCTGCCTTTGCATCAGACTCTCTAAGGACTGGAAGG  2600
806   P  A  R  E  A  A  F  A  S  D  S  L  R  T  G  R    821

2601 TCACGATCATCTCAGAGCATTTGTAAGGCAGGAGAAAGTACAGATGCCCT  2650
822  S  R  S  S  Q  S  I  C  K  A  G  E  S  T  D  A  L   838

2651 CAGCTTGCCTCATGTCAAACTGAAATAAGTTCTTCATTTTCTTTCCAGGC  2700
839   S  L  P  H  V  K  L  K                             846

2701 ATAGCAGTTCTTTAGCCATACATATCATTGCATGAACTATTTCGAAAGCC  2750

2751 CTTCTAAAAAGTTGAAATTGCAAGAATCGGGAAGAACATGAAAGGCAGTT  2800

2801 TATAAGCCCGTTACCTTTTAATTGCATGAAAATGCATGTTTAGGGATGGC  2850

2851 TAAAATTCCAAGGTGCATCGACATTAACCCACTCATTTAGTAATGTACCT  2900

2901 TGAGTTAAAAAGCCTGAGAAACCAAACACAGCTAATGCTATGGGGTGTAT  2950

2951 GAATATGTCAAGTTTAGGTCATTTAGAAGATTTGACACTGTATTTTGAAA  3000

3001 TTATGGGAGTAAACACCTTCAAATTTCAGGCATTTCTGCTTTGTGACTAA  3050

3051 ATACAAACTACATTTTCAAGATTAGGCCATAATGTATATTTAAACACAAT  3100

3101 GGCTATCAACAGCTGCTAATAAGGTATCAACTAAAGCAGAATTGGGGAAT  3150

3151 AATAGAAATGGCTGCTTATTTCAAGATATATTTGCCAACCCATTCCTATT  3200

3201 CAGTCATTTTATTATTAATGTAATTTGAATGTCAATTTGTGTGCTTTTGG  3250
```

FIGURE 2E

```
3251  TGATTTAGCGCTGTGGCAAGCAATTTTGCACATCATTTTCATGTTGTTCT  3300

3301  TTATGACAAGAATGTTCTTCAATTAGAAAATGTGCAAATAATGAAATTCA  3350

3351  GGGCCAGTGAGGCAAATAGACTATCTGACATATTTGACTTTATGAAAACA  3400

3401  TATTGCCTGATGGCAGAATCAACTTTATAAGTGGTCAACTTCTACACAAG  3450

3451  CGTATGAAATACTGGTCAGTAGAACAGCCATTGTGATTGGACTGGTTTCT  3500

3501  CTGCAATGGCGCCAACCCCAGGCTTGCCAATACTGCCTATGTAAAGGGCA  3550

3551  AGTGTGAGAAGCTATTCTCATTTCGCTGACATACAGGTAGGACTATGGGG  3600

3601  GATGGGACATTTGAGTGGGACTGAGATAGGAAAGGCTTGAAAAGAACCCA  3650

3651  GAAACACCACCAGGAAGTTGGCAAAGTAAAAGAAAATGACTTCCCCCTCA  3700

3701  AAGGGCAATGAGAGGGAG
```

FIGURE 3A

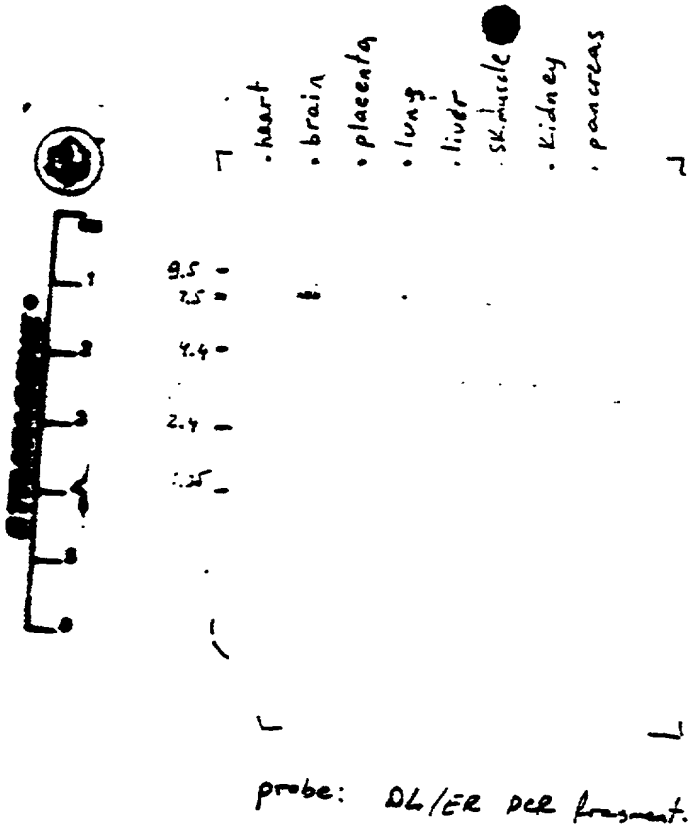

. heart
. brain
. placenta
. lung
. liver
. sk. muscle
. kidney
. pancreas
9.5
7.5
4.4
2.4
1.35
probe: DL/ER pcr fragment.

FIGURE 3B

RT-PCR analysis of the KCN6q gene expression in human tissues

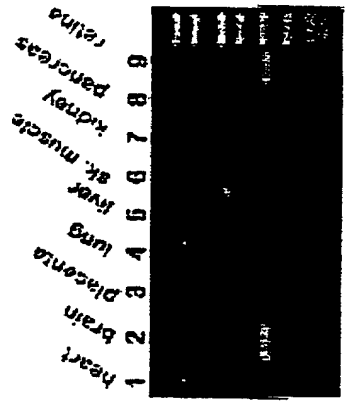


FIGURE 4A

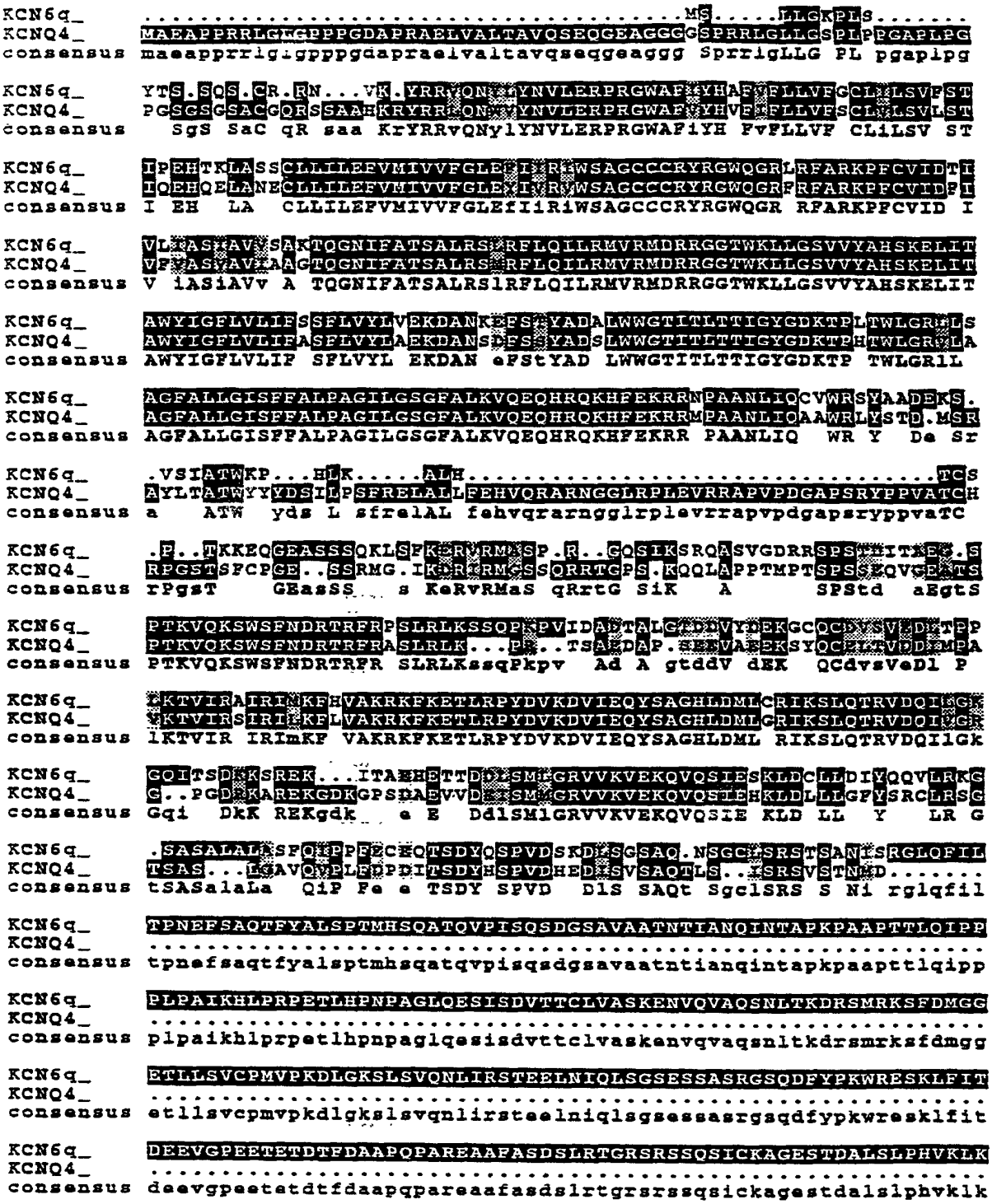


FIGURE 4B

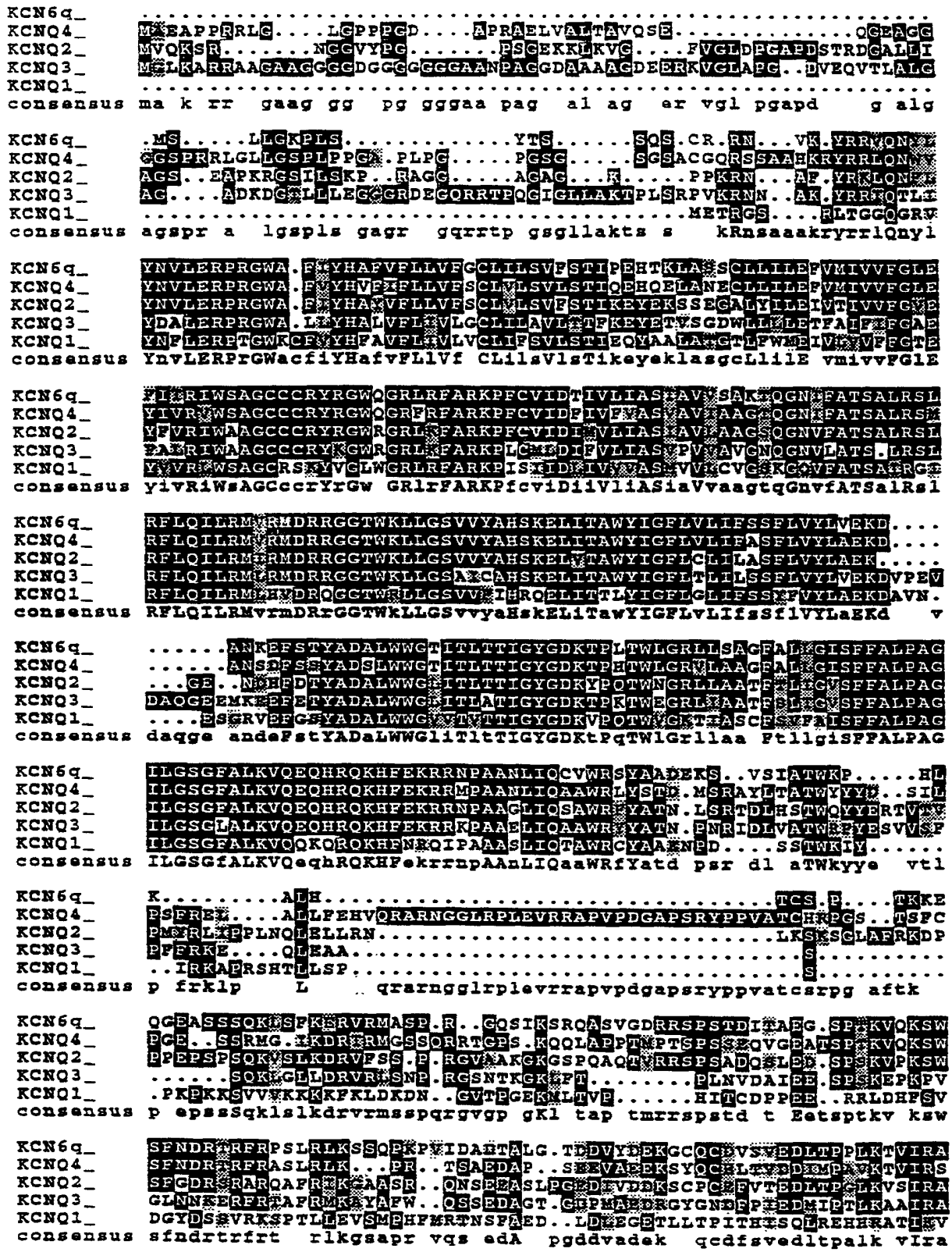
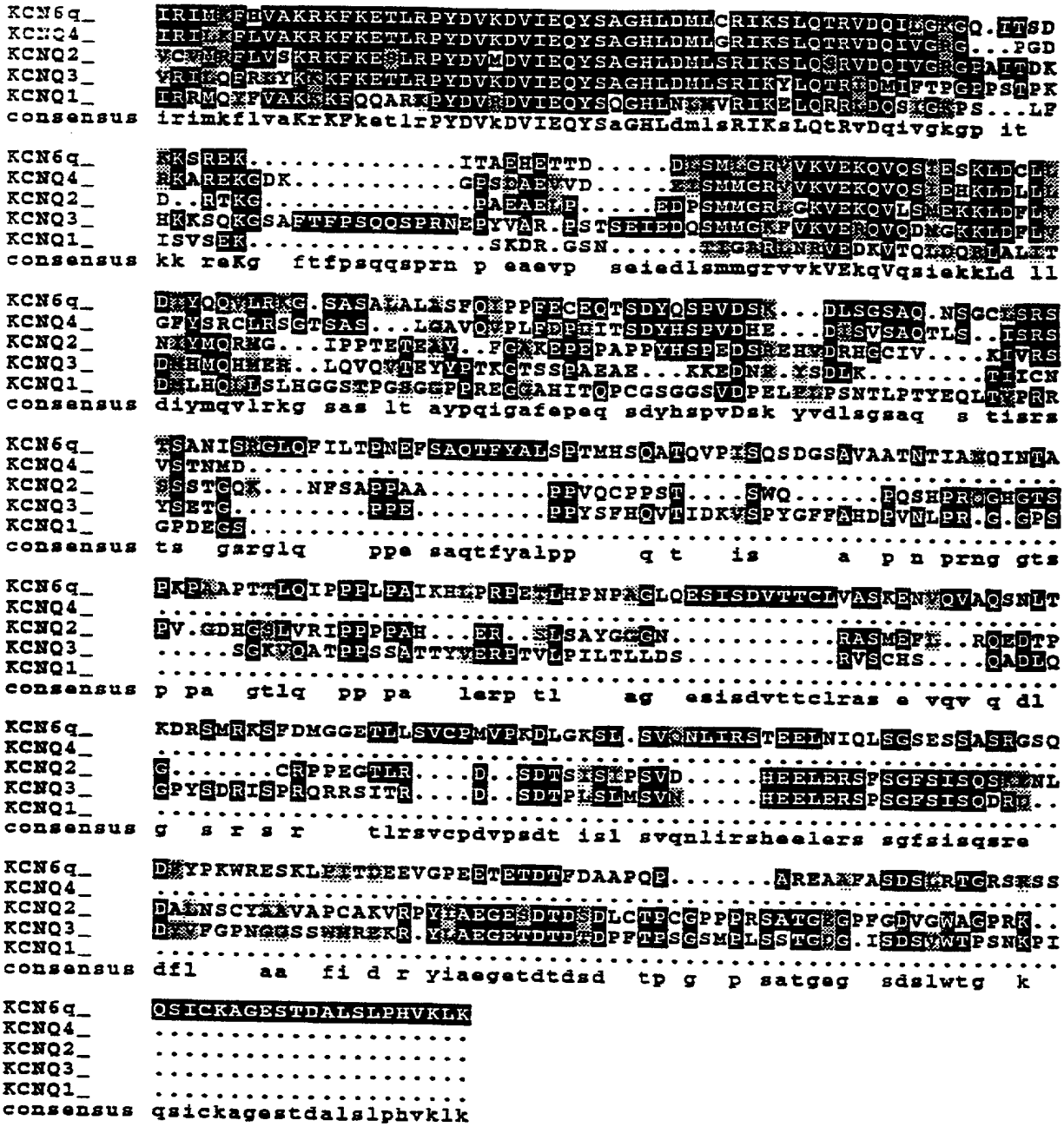


FIGURE 4C



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SUBSTITUTE for PTO/SB/01 (12-99), DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing **OR** ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	20430P
First Named Inventor	Petrukhin, et al.
COMPLETE IF KNOWN	
Application Number	09/937,499
Filing Date	September 26, 2001
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NOVEL HUMAN VOLTAGE-GATED POTASSIUM CHANNEL

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) 09/26/2001 as United States Application Number or PCT International Application Number [ ] and was amended on (MM/DD/YYYY) [ ] (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Attorney Docket Number	Priority Claimed? YES	NO
PCT/US00/09587	PCT	04/10/2000	20430-PCT	☒	☐
				☐	☐
				☐	☐
				☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	Attorney Docket Number
60/129,274	04/14/1999	20430PV

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SUBSTITUTE for PTO/SB/01 (12-97), DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY for Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information known to me to be material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Application Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)
PCT/US00/09587	04/10/2000	
60/129,274	04/14/1999	

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint, respectively and individually, as my attorneys or agents with full power of substitution and revocation, the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

☐ Customer Number [ ] → *Place Customer Number Bar Code Label here*

OR

[X] Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number
Joseph A. Coppola	38,413	Jack L. Tribble	32,633

Direct all correspondence to: [X] Customer Number or Bar Code Label 000210

Name	Joseph A. Coppola				
Address	Merck & Co., Inc. - Patent Department				
Address	P.O. Box 2000, RY60-30				
City	Rahway	**State**	NJ	**ZIP**	07065-0907
Country	USA	**Telephone**	(732)594-6734	**Fax**	(732)594-4720

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
KONSTANTIN	PETRUKHIN

Inventor's Signature					**Date**	December 6, 2001	
Residence: City	Collegeville PA.	**State**	PA	**Country**	US	**Citizenship**	RU
Post Office Address	Merck & Co., Inc., P.O. Box 2000						
City	Rahway	**State**	NJ	**ZIP**	07065-0907		

[X] Additional inventors are being named on the 1 supplemental Additional Inventors(s) sheet(s) PTO/SB/02A attached hereto.

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SUBSTITUTE for PTO/SB/02A (3-97), Declaration (Additional Inventors)

DECLARATION AND POWER OF ATTORNEY

ADDITIONAL INVENTOR(S)
Supplemental Sheet

Name of Additional Joint Inventor, if any:		☐ A petition has been filed for this unsigned inventor					
Given Name (first and middle [if any])				Family Name or Surname			
C. THOMAS				CASKEY			
Inventor's Signature				**Date**			
Residence: City	Lansdale	**State**	PA	**Country**	US	**Citizenship**	US
Post Office Address	Merck & Co., Inc., P.O. Box 2000						
City	Rahway	**State**	NJ	**ZIP**	07065-0907		
Name of Additional Joint Inventor, if any:		☐ A petition has been filed for this unsigned inventor					
Given Name (first and middle [if any])				Family Name or Surname			
WEN				LI			
Inventor's Signature				**Date**			
Residence: City	North Wales	**State**	PA	**Country**	US	**Citizenship**	US
Post Office Address	Merck & Co., Inc., P.O. Box 2000						
City	Rahway	**State**	NJ	**ZIP**	07065-0907		
Name of Additional Joint Inventor, if any:		☐ A petition has been filed for this unsigned inventor					
Given Name (first and middle [if any])				Family Name or Surname			
MICHAEL L.				METZKER			
Inventor's Signature				**Date**			
Residence: City	Fort Washington	**State**	PA	**Country**	US	**Citizenship**	US
Post Office Address	Merck & Co., Inc., P.O. Box 2000						
City	Rahway	**State**	NJ	**ZIP**	07065-0907		
Name of Additional Joint Inventor, if any:		☐ A petition has been filed for this unsigned inventor					
Given Name (first and middle [if any])				Family Name or Surname			
Inventor's Signature				**Date**			
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address	Merck & Co., Inc., P.O. Box 2000						
City	Rahway	**State**	NJ	**ZIP**	07065-0907		

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DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing **OR** ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	20430P
First Named Inventor	Petrukhin, et al.
COMPLETE IF KNOWN	
Application Number	09/937,499
Filing Date	September 26, 2001
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NOVEL HUMAN VOLTAGE-GATED POTASSIUM CHANNEL

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) 09/26/2001 as United States Application Number or PCT International Application Number [ ] and was amended on (MM/DD/YYYY) [ ] (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Attorney Docket Number	Priority Claimed? YES	NO
PCT/US00/09587	PCT	04/10/2000	20430-PCT	☒	☐
				☐	☐
				☐	☐
				☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

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SUBSTITUTE for PTO/SB/01 (12-97), DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY for Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application *is not disclosed in the prior United States* or PCT international application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information known to me to be material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Application Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*
PCT/US00/09587	04/10/2000	
60/129,274	04/14/1999	

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint, respectively and individually, as my attorneys or agents with full power of substitution and revocation, the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office *connected* therewith:

☐ Customer Number [ ] → *Place Customer Number Bar Code Label here*

OR

☒ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number
Joseph A. Coppola	38,413	Jack L. Tribble	32,633

Direct all correspondence to: ☒ Customer Number or Bar Code Label 000210

Name	Joseph A. Coppola				
Address	Merck & Co., Inc. - Patent Department				
Address	P.O. Box 2000, RY60-30				
City	Rahway	**State**	NJ	**ZIP**	07065-0907
Country	USA	**Telephone**	(732)594-6734	**Fax**	(732)594-4720

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
KONSTANTIN	PETRUKHIN

Inventor's Signature					**Date**		
Residence: City	Collegeville	**State**	PA	**Country**	US	**Citizenship**	RU
Post Office Address	Merck & Co., Inc., P.O. Box 2000						
City	Rahway	**State**	NJ	**ZIP**	07065-0907		

☒ Additional inventors are being named on the 1 supplemental Additional Inventors(s) sheet(s) PTO/SB/02A attached hereto.

Computer generated form " Declaration Pwr of Atty" (Application Filing Folder), Merck & Co., Inc. 04/05/2001

Please type a plus sign (+) inside this box → [+]

Approved for use through 9/30/2000. OMB 651-0032
SUBSTITUTE for PTO/SB/02A (3-97), Declaration (Additional Inventors)

DECLARATION AND POWER OF ATTORNEY

ADDITIONAL INVENTOR(S) Supplemental Sheet

2-00

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
C. THOMAS			CASKEY				
Inventor's Signature					**Date**	12/6/01	
Residence: City	Lansdale PA	**State** PA	**Country** US		**Citizenship** US		
Post Office Address	Merck & Co., Inc., P.O. Box 2000						
City	Rahway	**State** NJ	**ZIP** 07065-0907				
Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
WEN			LI				
Inventor's Signature					**Date**		
Residence: City	North Wales	**State** PA	**Country** US		**Citizenship** US		
Post Office Address	Merck & Co., Inc., P.O. Box 2000						
City	Rahway	**State** NJ	**ZIP** 07065-0907				
Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
MICHAEL L.			METZKER				
Inventor's Signature					**Date**		
Residence: City	Fort Washington	**State** PA	**Country** US		**Citizenship** US		
Post Office Address	Merck & Co., Inc., P.O. Box 2000						
City	Rahway	**State** NJ	**ZIP** 07065-0907				
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Given Name (first and middle [if any])			Family Name or Surname				
Inventor's Signature					**Date**		
Residence: City		**State**	**Country**		**Citizenship**		
Post Office Address	Merck & Co., Inc., P.O. Box 2000						
City	Rahway	**State** NJ	**ZIP** 07065-0907				

Please type a plus sign (+) inside this box → [+]

Approved for use through 9/30/2000. OMB 651-0032

SUBSTITUTE for PTO/SB/01 (12-97) DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing **OR** ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	20430P
First Named Inventor	Petrukhin, et al.
COMPLETE IF KNOWN	
Application Number	09/937,499
Filing Date	September 26, 2001
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NOVEL HUMAN VOLTAGE-GATED POTASSIUM CHANNEL

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) 09/26/2001 as United States Application Number or PCT International Application Number [ ] and was amended on (MM/DD/YYYY) [ ] (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Attorney Docket Number	Priority Claimed? YES	NO
PCT/US00/09587	PCT	04/10/2000	20430-PCT	☒	☐
				☐	☐
				☐	☐
				☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	Attorney Docket Number
60/129,274	04/14/1999	20430PV

Please type a plus sign (+) inside this box → [+]

Approved for use through 9/30/2000. OMB 651-0032

SUBSTITUTE for PTO/SB/01 (12-97), DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY for Utility or Design Patent Application

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OR

[X] Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number
Joseph A. Coppola	38,413	Jack L. Tribble	32,633

Direct all correspondence to: [X] Customer Number or Bar Code Label 000210

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Address	Merck & Co., Inc. - Patent Department						
Address	P.O. Box 2000, RY60-30						
City	Rahway			**State**	NJ	**ZIP**	07065-0907
Country	USA	**Telephone**	(732)594-6734			**Fax**	(732)594-4720

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Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
KONSTANTIN	PETRUKHIN

Inventor's Signature						**Date**	
Residence: City	Collegeville	**State**	PA	**Country**	US	**Citizenship**	RU
Post Office Address	Merck & Co., Inc., P.O. Box 2000						
City	Rahway			**State**	NJ	**ZIP**	07065-0907

[X] Additional inventors are being named on the 1 supplemental Additional Inventors(s) sheet(s) PTO/SB/02A attached hereto.

Please type a plus sign (+) inside this box → [+]

Approved for use through 9/30/2000. OMB 651-0032
SUBSTITUTE for PTO/SB/02A (3-97), Declaration (Additional Inventors)

DECLARATION AND POWER OF ATTORNEY

ADDITIONAL INVENTOR(S)
Supplemental Sheet

Name of Additional Joint Inventor, if any:		☐ A petition has been filed for this unsigned inventor					
Given Name (first and middle [if any])		Family Name or Surname					
C. THOMAS		CASKEY					
Inventor's Signature					**Date**		
Residence: City	Lansdale	**State**	PA	**Country**	US	**Citizenship**	US
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Name of Additional Joint Inventor, if any:		☐ A petition has been filed for this unsigned inventor					
Given Name (first and middle [if any])		Family Name or Surname					
WEN WEN		LI LI					
Inventor's Signature					**Date**	12/10/2001	
Residence: City	North Wales PP.	**State**	PA	**Country**	US	**Citizenship**	US
Post Office Address	Merck & Co., Inc., P.O. Box 2000						
City	Rahway	**State**	NJ	**ZIP**	07065-0907		

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MICHAEL L.		METZKER					
Inventor's Signature					**Date**		
Residence: City	Fort Washington	**State**	PA	**Country**	US	**Citizenship**	US
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First Named Inventor	Petrukhin, et al.
COMPLETE IF KNOWN	
Application Number	09/937,499
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Group Art Unit	
Examiner Name	

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(Title of the Invention)

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PCT/US00/09587	PCT	04/10/2000	20430-PCT	☒	☐
				☐	☐
				☐	☐
				☐	☐

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Given Name (first and middle [if any])	Family Name or Surname
KONSTANTIN	PETRUKHIN

Inventor's Signature					**Date**		
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Post Office Address	Merck & Co., Inc., P.O. Box 2000						
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DECLARATION AND POWER OF ATTORNEY

ADDITIONAL INVENTOR(S)
Supplemental Sheet

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Given Name (first and middle [if any])		Family Name or Surname					
C. THOMAS		CASKEY					
Inventor's Signature					**Date**		
Residence: City	Lansdale	**State**	PA	**Country**	US	**Citizenship**	US
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WEN		LI					
Inventor's Signature					**Date**		
Residence: City	North Wales	**State**	PA	**Country**	US	**Citizenship**	US
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MICHAEL L.		~~METZKER~~					
Inventor's Signature					**Date**	12/10/2001	
Residence: City	Fort Washington PA	**State**	PA	**Country**	US	**Citizenship**	US
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